University of Alberta

The Risk of Breast Cancer From Hormone Replacement Therapy Combined with Mammographic Radiation Exposure

by

Carl David Schumaker ©

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Master of Science

Department of Radiology and Diagnostic Imaging

Edmonton, Alberta
Spring 1999

National Library
of Canada

Acquisitions and
Bibliographic Services

395 Wellington Street
Ottawa ON K1A 0N4
Canada

Bibliothèque nationale
du Canada

Acquisitions et
services bibliographiques

395, rue Wellington
Ottawa ON K1A 0N4
Canada

Your file Votre référence

Our file Notre référence

The author has granted a non-exclusive licence allowing the National Library of Canada to reproduce, loan, distribute or sell copies of this thesis in microform, paper or electronic formats.

L'auteur a accordé une licence non exclusive permettant à la Bibliothèque nationale du Canada de reproduire, prêter, distribuer ou vendre des copies de cette thèse sous la forme de microfiche/film, de reproduction sur papier ou sur format électronique.

The author retains ownership of the copyright in this thesis. Neither the thesis nor substantial extracts from it may be printed or otherwise reproduced without the author's permission.

L'auteur conserve la propriété du droit d'auteur qui protège cette thèse. Ni la thèse ni des extraits substantiels de celle-ci ne doivent être imprimés ou autrement reproduits sans son autorisation.

0-612-40106-5

Canada

University of Alberta

Library Release Form

Name of Author: Carl David Schumaker

Title of Thesis: The Risk of Breast Cancer From Hormone Replacement Therapy Combined with Mammographic Radiation Exposure

Degree: Master of Science

Year this Degree Granted: 1999

Permission is hereby granted to the University of Alberta Library to reproduce single copies of this thesis and to lend or sell copies for private, scholarly, or scientific research purposes only.

The author reserves all other publication and other rights in association with the copyright in the thesis, and except as hereinbefore provided, neither the thesis nor any substantial portion thereof may be printed or otherwise reproduced in any material form without the author's prior written permission.

Carl D Schumaker

#141, 10633 - 31 Avenue
Edmonton, Alberta T6J 4N4

Date Submitted: 20 April 1999

University of Alberta
Faculty of Graduate Studies and Research

The undersigned certify that they have read, and recommended to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled **The Risk of Breast Cancer from Hormone Replacement Therapy Combined with Mammographic Radiation Exposure**, submitted by Carl D. Schumaker in partial fulfillment of the requirements for the degree of Master of Science.

Dr. L.J. Filipow (Supervisor)

Dr. A.J.B. McEwan

N Horeczko
Dr. N. Horeczko

H Bryant
Dr. H. Bryant

Dated: 20 April 99

ABSTRACT

Previous studies of the relative risk of breast cancer from hormone replacement therapy (HRT) have taken into account possible confounding by age, reproductive history, breast history and type of menopause. In addition to these factors, this study accounted for possible confounding by mammographic radiation exposure and tested for interaction between mammographic radiation exposure and HRT use.

The study included women age 60 years and older who had sufficient radiological indications for a breast biopsy. The likelihood of a positive diagnosis of breast cancer associated with current HRT use and mammographic radiation exposure was estimated using a case-control design and involved 2,110 postmenopausal women who had received breast biopsies at a breast imaging clinic between 1989 and 1998.

Women who reported current hormone replacement therapy in the study population were found to be less likely to be diagnosed with a malignant breast cancer than women who reported no current HRT use. Also, women who had received mammographic radiation exposure one year or more from the date of diagnosis were less likely to be diagnosed with a malignant breast cancer than women who had not received any past mammographic exposure. However, no interaction was found between mammographic exposure and current HRT use affecting the likelihood of a woman in the study population receiving a diagnosis of breast cancer.

?

Acknowledgment

The author wishes to thank Dr. Natalka Horeczko for allowing the patient charts at the Lendrum Breast Clinic to be used in this study. Without her interest, advice and kind assistance, this project would not have been possible. Thanks also goes to Dr. Heather Bryant for her many helpful suggestions on the research design and epidemiological considerations of the study. Also, the author thanks Dr. A.J. B. (Sandy) McEwan for his words of encouragement and help in defining the objectives of the study and to Dr. Nancy Lovell for her advice, support and friendship throughout the study. The author also wishes to thank his children Kacey, Dustin and Angeline for their love, patience and understanding, and to Felina for her constant support and affection throughout the study. Finally, the author wishes to thank his friend and project supervisor, Dr. Larry Filopow for his continual support and encouragement, as well as the many helpful suggestions and advice that he provided.

Table of Contents

CHAPTER 1 INTRODUCTION:

Proposal 1

Rationale and Significance of the Problem 2

Statement of the Problem 3

General Hypothesis 4

Definitions 5

Summary and Overview 11

CHAPTER 2 LITERATURE REVIEW:

Introduction 13

Summary of Risk Factors for Breast Cancer 13

Results of Risk Factor Investigations 16

The Risk of Breast Cancer from Ionizing Radiation 17

The Risk of Breast Cancer from HRT 30

Summary 36

CHAPTER 3 METHOD:

Introduction 38

Study Population 38

Data Sources 41

Data Collection Procedures 52

Research Design 58

Research Hypothesis 62

Treatment of the Data 62

Limitations of the Study 64

Summary 68

CHAPTER 4 RESULTS:

Introduction 69

Selection of Risk Factors 69

Fitting the Multivariate Logistic Regression Model 73

Test for Interaction 74

Model for Invasive Breast Cancer in the Study Population ..76

Hormone Type and Stage of Disease Effects 76

Summary 78

CHAPTER 5 DISCUSSION AND CONCLUSIONS:

Overview of the Study 81

Overview of the Results 82

Summary and Conclusions 101

Future Work 104

TABLES 106

FIGURES 125

REFERENCES 137

APPENDICES:

A Average Glandular Dose Determination 150

B Data Collection Instructions 155

List of Tables

1 Studies of Breast Cancer Risk Associated with Hormone Replacement .. 107

2 Relative Risk of Breast Cancer Associated with Hormone Replacement Therapy Estimated by Different Diagnostic Methods and Types of Controls .108

3 Relative Risk of Breast Cancer Assoicated with Hormone Replacement Therapy (meta-analysis results from this study) 109

4 General Format of Contingency Table Used in the Study. 110

5 Percentage of Selected Characteristics Among Invasive Breast Cancer Cases and Controls 111

6 Distribution of HRT Duration Among Breast Cancer Cases and Controls .. 112

7 Distribution of Cumulative Breast Dose Among Breast Cancer Cases and Controls 113

8 Code for the Study Variables 114

9 Univariate Logistic Regression Models for Invasive Breast Cancer 115

10 Multivariate Model Containing Biologically Important Variables or Variable Indentified as Significant in the Univariate Analysis 116

11 Log-likelihood Ratio Test Statistic for the Addition of Interaction Terms to the Main Effects Model 117

12 Relative Risk of Invasive Breast Cancer Associated with Current HRT Use of Any Duration (stratified by cumulative mammographic radiation dose) .. 118

13 Relative Risk of Invasive Breast Cancer Associated with Mammographic Radiation Dose (stratified by HRT use) 119

14 Multivariate Model with Significant Interaction Terms Included 120

15 Relative Risk of Invasive Cancer Stratified by HRT Type 121

16 Relative Risk of Invasive Breast Cancer Stratified by HRT Type and Stage of Disease 122

17 Relative Risk of Invasive Breast Cancer Associated with Current HRT Use Stratified by Tumour Size 123

18 Invasive Tumour Size Distribution Among Current Users and Nonusers of HRT 124

List of Figures

1 Mean Relative Risk of Breast Cancer for 'Ever Use' Hormone Replacement Therapy from Meta-Analysis 126
2 Study Population 127
3 Patient History Form 128
4 Radiology Report 129
5 Surgical Pathology Report 130
6 Patient Data Summary Form 132
7 Breast Dose vs Compressed Breast Thickness 133
8 Entrance Skin Exposure vs X-Ray Machine Settings 134
9 Exposure-Dose Ratio vs Compressed Breast Thickness 135
10 Relative Risk of Invasive Breast Cancer Associated with Cumulative Breast Dose 136

Chapter 1

Introduction

A. Proposal:

Ionizing radiation exposure has been shown to be a risk factor for the development of various forms of cancer in humans including breast cancer (NRC 1990). Studies which have demonstrated the carcinogenic effect of ionizing radiation in human breast tissue include female patients exposed to large doses of ionizing radiation through fluoroscopy (Myrden 1969, Hrubec 1989, Miller 1989, Boice 1991) , women treated for acute postpartum mastitis (Shore 1986), and studies of atomic bomb survivors (Land 1979,Tokunaga 1987, McGregor 1977, Tokunaga 1994, Goodman 1997).

The mechanism by which ionizing radiation causes cancer is thought to be by initiation of a genetic mutation. The mutated cell may lie dormant or may be stimulated to divide through the action of promoting agents. Certain hormones are suspected to be promoters of cancer including estrogen (NCR 1990).

In 1989, the Radiation Effects Research Foundation published a study which found that prepubescent women who were exposed to atomic bomb radiation had an increased risk of breast cancer after puberty and the earlier the age at radiation exposure the greater the risk (Tokunaga 1987). The authors of this study hypothesized that endogenous estrogen was promoting the carcinogenic effect of ionizing radiation in these prepubescent women and that the younger the age at exposure, the longer the period of endogenous estrogen promotion, and the greater the risk of breast cancer.

An additional finding by the Radiation Effects Research Foundation was that women over the age of 50 at the time of exposure to atomic bomb radiation did not show an increased risk of breast cancer (Tokunaga 1987). The authors suggested that although ionizing radiation may have initiated the carcinogenic process in the breast tissues of older women, the absence of sufficient levels of estrogen prevented the subsequent promotion and development of breast cancer. If this hypothesis is correct, postmenopausal women who have received radiation dose to the breast may have a greater risk of breast cancer if they are receiving hormone replacement therapy.

The objective of this study is to test this hypothesis by comparing the risk of breast cancer in postmenopausal women who have been exposed to different levels of mammographic radiation and who have had different histories of hormone replacement therapy.

B. Rationale and Significance of the Problem:

A number of studies have been conducted to determine if exogenous estrogen has the potential to cause breast cancer. These studies have included women using oral contraceptives (White 1984, Romieu 1989, Brinton 1995, Rossing 1996) and women treated for postmenopausal symptoms by estrogen replacement therapy (Hoover 1976, Colditz 1995, Brinton 1993). The results of these studies have been mixed, but there is evidence for a small elevated risk of breast cancer from long term (greater than 10 years) estrogen replacement suggesting that an extended promotional period is required for the expression of breast cancer (Pike 1993, Brinton 1993).

In the last ten years, the practice of prescribing estrogen-progestin rather than estrogen alone for women who have not received a hysterectomy has become increasingly common (Stanford 1993). The antiestrogenic effect of progesterone on endometrial tissue has been found to reduce the risk of endometrial cancer associated with estrogen replacement therapy (Pike 1993). The addition of progestin to estrogen in hormone replacement therapy (HRT) may also affect the risk of breast cancer, and a number of recent studies have attempted to estimate the risk of breast cancer from estrogen-progestin use (Colditz 1995, Risch 1994).

If the carcinogenic effects of HRT are limited to the promotion of breast cancer and not its initiation, then it is possible that only women who have been exposed to initiators of breast cancer would be at elevated risk from HRT use (NRC 1990). The failure of some studies to detect an increase in the risk of breast cancer from HRT use may be a result of including women in the study who were not exposed to initiators of breast cancer and therefore were not at risk from HRT exposure. Also, if the effect of estrogen or progesterone is limited to promoting or causing the progression of breast cancer, this should be considered in the design of the study. The type and stage of breast cancer should be taken into account when defining the risk to be measured.

Another reason for taking into account past radiation exposure in risk assessment studies of HRT is to control for potential confounding. Women who receive HRT may have mammograms taken more frequently and consequently may receive more radiation exposure to the breast than women not receiving HRT. Since radiation exposure is a known risk factor for breast cancer, it may be contributing to the elevated risk in long duration HRT use. Therefore the potential confounding effect of radiation exposure should be controlled in a risk assessment of HRT. This study attempted to control for the possible confounding effects of radiation exposure in estimating the risk of breast cancer from HRT use in postmenopausal women.

C. Statement of the Problem:

Previous studies assessing the risk of breast cancer from HRT use or mammographic radiation exposure have performed subgroup analyses based on age, race, menopausal status, ovarian status, parity, menstrual history, breast history and type of hormone preparation (NRC 1990, Brinton 1993). In addition to considering these subgroups, this study performed an analysis of the HRT risk of breast cancer in the context of mammographic radiation exposure subgroups and an analysis of the radiation risk of breast cancer in the context of HRT subgroups. It examined the potential confounding or modifying effects of mammographic radiation exposure on the risk of breast cancer from current HRT use and the potential confounding or modifying effects of HRT use on the risk of breast cancer from mammographic radiation exposure.

This was accomplished in a case-control study by estimating the relative risk of breast cancer from different combinations of HRT use and cumulative breast dose while taking into account the type of hormone and stage of disease. The type of hormone and stage of disease was also taken into account to identify any changes in risk with these factors.

D. General Hypothesis:

It is hypothesized that the odds ratio of breast cancer from mammographic radiation exposure is modified by the duration of current HRT use.

$$H_0: OR_x = OR_y \qquad \text{vs} \qquad H_1: OR_x \neq OR_y$$

Where OR_x equals the odds ratio of breast cancer from mammographic radiation exposure and current HRT use of duration x and OR_y equals the odds ratio of breast cancer from mammographic radiation exposure and current HRT use of duration y. It is also hypothesized that the odds ratio of breast cancer from hormone replacement therapy (HRT) is modified by radiation exposure received from mammography.

$$H_0: OR_n = OR_m \qquad \text{vs} \qquad H_1: OR_n \neq OR_m$$

Where OR_n equals the odds ratio of breast cancer from current HRT use and mammographic dose of level n and OR_m equals the odds ratio of breast cancer from current HRT use and mammographic dose of level m.

E. Definitions:

The following operational definitions are given of the key terms and concepts used in this study:

1. *Cancer*: A malignant tumour of potentially unlimited growth, capable of invading surrounding tissue or spreading to other parts of the body by metastasis (NRC 1990).

2. *Benign Breast Disease:* Benign breast disease includes a variety of conditions including benign tumours such as adenomas arising from glandular tissue, fibromas arising from fibrous tissue and lipomas arising from fat cells. Benign breast disease also includes cysts, duct ectasia (inflamed ducts), epithelial hyperplasia (overgrowth of cells lining the ducts) and duct papillomas (benign wart-like growths) (Kelly 1991, Hayes 1993).

3. *Bias:* Any difference between the true value and the value actually obtained which is due to causes other than sample variation. It is also referred to as systematic error. A variety of different types of bias may exist in any epidemiologic study, however case-control studies are particularly prone to this type of error (Henekens 1987).

Misclassification bias refers to error in the classification of study subjects with respect to some characteristic such as the disease or exposure of interest. When the frequency of this type of error differs between cases and controls the bias is termed 'differential'. When the frequency of the error is the same for cases and controls, the bias is termed 'random' or 'non differential'.

Observer or detection bias refers to a difference in the manner in which exposure, disease or other information is collected on cases and controls. It can affect both the magnitude and direction of the estimate of risk.

Recall bias refers to differences in the accuracy with which study subjects remember information on past exposures or other characteristics of interest. For instance, when patients are aware of their disease status, it may affect their ability to recall information on past exposures which could effect the outcome of the study.

Selection bias refers to differences in the manner in which study subjects are selected which may be associated with the exposure of interest. For example, selection bias occurs if study subjects are selected based on characteristics which correlate with the exposure of interest, and these characteristic differ among cases and control.

Surveillance bias is similar to detection bias but specifically refers to differences in the diagnostic criteria or technique applied, based on differences in exposure history. For example, if some study subjects are more rigorously examined for the presence of disease based on knowledge of their exposure to some agent, a biased correlation may be observed between the disease and exposure to the agent.

4. *Breast Cancer*: Cancer in the breast tissue that originated in the breast and not simply a secondary spread of cancer from other tissues in the body (Vorherr 1980). There are a number of different types of breast cancer depending on which type of tissue in the breast the cancer originated.These would include ductal carcinoma, the most common type of breast cancer originating from epithelial cells of breast ducts; lobular carcinoma, originating from epithelial cells of breast lobules; and rarer forms of breast cancer such as sarcomas, arising from connective tissue cells (Hayes 1993).

Both ductal carcinoma and lobular carcinoma can occur in two forms; in situ carcinoma which is breast cancer that is confined to the duct or lobule and shows no evidence of invasion to surrounding tissue; invasive carcinoma in which the tumour has spread beyond the duct or lobule into surrounding tissue within the breast or beyond (Hayes 1993).

5. *Confounding:* When an apparent association between a suspected risk factor and a disease is due to a third agent which is associated with the suspected risk factor but independently affects the risk of developing the disease. The third factor in this case is

called a 'confounding factor'. Confounding occurs most commonly when there is some difference between the groups under study other than the risk factor of interest, which affects the risk of developing the disease (Hennekens 1987).

6. *Effect Modification:* A change in magnitude or direction of association between the exposure of interest and the disease due to the presence or change in level of a third factor. When this occurs, the factor is considered to be an 'effect modifier' of the association between the exposure and the disease (Hennekens 1987).

7. *Generalizability :* The extent to which the results of the study can be applied to populations other than the study population (Last 1983).

8 *Hormone Replacement Therapy (HRT)*: HRT is the administration of hormones to women who are menopausal or postmenopausal and are experiencing symptoms related to a decrease in the ovarian production of estrogen. The hormone treatment is intended to supplement or replace the falling levels of estrogen and thereby decrease or eliminate the symptoms. The types of hormones given include synthetic estrogen, conjugated estrogens of equine origin and combined estrogen-progestin preparations (Baum 1994).

9. *Menopause*: Menopause is the cessation of the menstrual cycle and the disappearance of menstruation. The average age of menopause is 51 years and is due to a gradual decrease in the level of ovarian estrogen and the ovarian response to stimulation by gonadotropins of the hypothalamus. Although menstruation is a normal event in a woman's life, it can occur either naturally between the ages of 45 and 55 or surgically by hysterectomy, ovariectomy or both.

Prior to menopause, women go through a period of gradual declining ovarian function called the climacteric or perimenopausal period. Menopause is followed by a period known as postmenopause in which the primary hormones produced by the ovaries are testosterone and androstenedione. The latter androgen undergoes peripheral conversion to estrone which is the major postmenopausal estrogen (Donegan 1988).

10. *Ionizing Radiation Exposure / Absorbed Dose*: Radiation exposure is a measure of the amount of ionization per unit mass of air (coulomb per kilogram) due to x-rays or gamma rays and is usually measured in units of roentgen (NRC 1990). In radiology this is also referred to as 'entrance skin exposure' or simply 'entrance exposure' which is the exposure at the surface of the patient (e.g. breast surface) (Bushberg 1994).

Radiation Absorbed Dose is the amount of energy absorbed per unit mass of tissue from ionizing radiation penetrating the tissue and is referred to as 'absorbed dose'. Absorbed dose is measured in units of radiation absorbed dose (rad) or in units of gray, where 100 rad is equivalent to 1 gray (NRC 1990).

In calculating the absorbed dose to the breast from a measured skin exposure, the tissue which is of most concern with respect to carcinogenesis is glandular tissue (Bushberg 1994). Depending on the depth of glandular tissue within the breast, the glandular tissue will receive varying amounts of absorbed dose for a given entrance skin exposure. However the 'average glandular dose' referred to as D_g, can be calculated from the entrance skin exposure, X_{ese}, using a conversion factor, D_{gn}, which has been determined experimentally and through computer simulations (Bushberg 1994). The value of D_{gn} depends on a number of factors including breast thickness, breast composition, quality of the radiation (i.e. penetrating ability), as well as the x-ray tube target material which determines the energy spectrum of the x-rays produced (Bushberg 1994). Hence, $D_g = D_{gn} \times X_{ese}$.

Tables and graphs are available in the literature for values of D_{gn} or which provide D_g directly for different values of X_{ese}, compressed breast thickness and tube material (Wu 1991). The Xese value depends on the time required to achieve a certain optical density on the mammographic film which is determined by the automatic exposure control device on the x-ray equipment (Bushberg 1994). This varies with compressed breast thickness, peak kilovoltage and milliampere values used in the exposure (Bushberg 1994).

11. *Risk*: Risk is defined as the probability that an individual will become ill or die within a stated period of time or age (Last 1983). Risk can be measured in absolute terms or in relative terms, the former called the absolute risk and latter called the relative risk (Last 1983).

To measure absolute risk the incidence rate of morbidity or mortality of a certain disease in the control population, I_u, is subtracted from the incidence rate of morbidity or mortality of the disease in a population exposed to the agent suspected of having a causal relationship with the disease, I_e. The difference in these two incidence rates, $I_e - I_u$, is due to the suspected agent and is measured in deaths or cases per 10^6 per year (Hennekens 1987, Kahn 1989).

The relative risk is the ratio of the incidence rate in the exposed population, I_e, to the incidence rate in the unexposed or control population, I_u, where relative risk equals I_e / I_u (Hennekens 1987). While the absolute risk measures the magnitude of the risk or probability of death or disease from exposure to a certain agent, the relative risk is unitless and is a measure of the likelihood that the exposed population will develop the disease or die from the disease relative to the unexposed group (Hennekens 1987).

In case-control studies the odds ratio is used as an estimate of the relative risk since the incidence rates, I_e and I_u, cannot be directly determined (Hennekens 1987, Kahn 1989). The odds ratio is defined as the ratio of the odds of diseased persons having been exposed to the agent of interest, to the odds of healthy persons having been exposed to the agent of interest (Hennekens 1987, Kahn 1989). That is,

$$\text{odds ratio} = \frac{\text{number of cases exposed} + \text{number of cases not exposed}}{\text{number of controls exposed} + \text{number of controls not exposed}}$$

The odds ratio is often a good approximation of the relative risk provided that the disease is rare in the population and in many studies the term odds ratio is synonymous with relative risk (Hennekens 1987, Kahn 1989).

12. *Mammography*: One of the imaging techniques used for detecting breast pathology is mammography. Mammography specifically utilizes x-rays to image the breast in conjunction with film, film-screen, or other detection techniques. Mammography is one of a number of modalities used in radiology and depends upon the use of specialized x-ray equipment dedicated to breast imaging (Bushberg 1994). Mammography is used for the diagnosis of breast cancer in symptomatic women and as a screening test for breast cancer in asymptomatic women (Zhou 1989).

The detection of a breast lesion depends on the differential radiation absorption and subsequent film contrast differences between the lesion and surrounding breast tissue. Mammography is particularly useful for detecting occult lesions that are not palpable during physical examination. Most lesions smaller than 1 to 2 cm in diameter are not palpable except in small breasts or if the lesion is just below the skin (Zhou 1989). Mammography however, can detect lesions as small as 0.1 cm, microcalcifications as small as 100 μm and is especially accurate in imaging breasts of low density were adequate film contrast between the lesion and surrounding skin can be expected.

13. *Reliability.* The degree of stability exhibited when a measurement (e.g. response to questionnaire) is repeated under identical conditions (Last 1983).

14. *Validity.* The degree to which a measurement, measures what it purports to measure (i.e. accuracy) (Last 1983). There are several ways that the validity of a measurement can be evaluated.

Construct validity refers to the extent to which the measurement corresponds to theoretical concepts concerning the phenomenon under study. For example, oral temperature measurement has good construct validity for predicting viral infection since viral infection generally results in elevated body temperature.

Content validity is the extent to which the measurement incorporates the domain of the phenomenon. For example, if a set of questions are asked concerning the history of benign breast disease, they have content validity if they adequately cover the various types of benign breast disease.

Criterion validity is the extent to which the measurement correlates with an external criterion (i.e. a medical test) of the phenomenon. For example, if a patient reports chronic fatigue, this would have high criterion validity for predicting anemia if subsequent medical tests indicated anemia .

F. Summary and Overview:

Radiation exposure has been shown through epidemiologic studies to be a carcinogen and a risk factor for breast cancer (NRC 1990). Estrogen however, is suspected to be a substance which promotes breast cancer only after the initial induction of cancer by a carcinogen such as ionizing radiation (NRC 1990). Studies of the risk of breast cancer associated HRT use have been inconclusive, with some showing a slightly elevated risk from long term use and others showing no risk of breast cancer from HRT use (Steinberg 1994).

If estrogen is a promoting agent for breast cancer, its effect may be contingent on sufficient prior exposure to a carcinogen such as ionizing radiation. Therefore studies which do not account for differences in prior carcinogenic exposure among the study population, may fail to detect any increased risk from exogenous estrogen use.

If estrogen promotes breast cancer, women may have a greater risk of breast cancer from mammographic radiation exposure if they are HRT users. Furthermore, HRT users may be at greater risk of developing breast cancer if they receive sufficient levels of radiation dose to the breast. Women who receive moderate to large doses of radiation to the breast might show an increased risk of breast cancer only after HRT use. Furthermore, the slightly increased relative risk of breast cancer from long term HRT use may be due to an accumulation of mammographic radiation dose during a period of prolonged promotional opportunity for carcinogenesis.

In summary, this study attempts to identify an interaction between HRT and ionizing radiation by comparing the relative risk of breast cancer for different levels of mammographic radiation dose and HRT use. The next chapter will provide a review of the existing literature on the risk of breast cancer from ionizing radiation and HRT use.

Chapter 2

Literature Review

A. Introduction:

This chapter will provide a review of the major studies which have attempted to elucidate the etiology of breast cancer with emphasis on the role of radiation and estrogen as risk factors. It will begin with a review of the various risk factors which have been investigated and then look specifically at those studies which have provided estimates of the risk from radiation exposure and hormone replacement therapy. The objective of this chapter is to summarize the work which has been done to date on the risk of breast cancer from ionizing radiation exposure and hormone replacement therapy.

B. Summary of Risk Factors for Breast Cancer:

Breast cancer is a significant disease which strikes one in ten women and is a major health issue (Gail 1989, Feur 1993). Consequently, a large number of studies have been conducted to examine suspected risk factors for breast cancer and these studies have been extensively reviewed elsewhere (MacMahon 1973, Kelsey 1988, Stoll 1989, Willet 1989, Hayes 1993). In particular, such factors as age (Pike 1983), diet (Willett 1987, Londen 1989, Howe 1990, Kushi 1992, Freedman 1993, Kushi 1996), reproductive history (Dupont 1987, White 1987, Kampert 1988, Iqbal 1989, Newcomb 1994, Daling 1996), race (Nataragan 1985, Ownby 1985, Barton 1987, Mettlin 1989), socioeconomic status (Mettlin 1989, Barton 1987), personal history and family history of breast cancer (Swift 1987, Dupont 1987, Lynch 1989, Jenks 1994), alcohol use (Willett 1987), tobacco use (Morabia 1996), pesticide exposure (Krieger

1994), benign and proliferative breast disease (Dupont 1985, Dupont 1987, Dupont 1989), mammographic density and parenchymal patterns (Berkowitz 1990, Laya 1995), body shape, size, and composition (Londen 1989, Tretli 1989, Harris 1992, Ballard 1990, Zhang 1996, Yong 1996), age at menarche and menopause (Trichopoulos 1972, Kampert 1988), and oral contraceptive use (White 1984, Romieu 1989, Brinton 1995, Rossing 1996) have all been examined as possible risk factors breast cancer.

In addition to these factors, hormone replacement therapy (HRT) and ionizing radiation exposure have also been extensively investigated for their potential to cause breast cancer. This includes several major reviews and meta-analyses on the role of HRT and breast cancer (Armstrong 1988, Steinberg 1991, Sillero-Arenas 1992, Steinberg 1994, Heinrick 1992, Brinton 1993, Stanford 1993) and the radiation related risks of breast cancer (Baral 1977, Mole 1978, Land 1980, Fry 1986, Zhou 1989, NRC 1990, ICRP 1991, Upton 1991,Schneider 1995).

The mechanism by which radiation exposure leads to carcinogenesis has been suggested to be a three stage process of initiation, promotion and progression (Moolgavkar 1980, Moolgavkar 1981, Jaffe 1986, NRC 1990). Ionizing radiation is thought to initiate the carcinogenic process by either altering the structure of DNA or by causing changes in gene expression leading to a cell line with the potential for unrestrained growth and proliferation (Jaffe 1986, NRC 1990). The expression of this potential occurs in the second and third step of carcinogenesis in which a promoting agent stimulates the preneoplastic cell to divide. After many successive cell divisions, the original cell line eventually progresses to a malignant phenotype capable of evading the host's defence mechanisms resulting in a tumour that has metastasized (NRC 1990, Bushberg 1994). Ionizing radiation has been shown to be capable of also promoting carcinogenesis and enhancing its progression (Jaffe 1988).

In addition to ionizing radiation other agents are capable of initiating, promoting or causing the progression of the carcinogenic process. Unlike ionizing radiation however, some agents are capable of promoting carcinogenesis but are apparently incapable of initiating it. Estrogen is thought to be in that category of agents whose role is limited to the promotion of cancer (Henderson 1988, NRC 1990).

The initiation of cancer in the breast seems to be dependent on the number of target cells and the degree of differentiation at the time of radiation exposure. Evidence of this comes from studies showing that early pregnancy, multiple pregnancies, and lactation which increase the degree of differentiation of cells in the breast by the action of prolactin, reduce the risk of breast cancer (Tricholopoulos 1972, Pike 1983, Dupont 1987, White 1987, Kampert 1988, Iqbal 1989,Newcomb 1994). Conversely, those conditions which increase mitotic activity or reduce the degree of cellular differentiation in the breast seem to increase the risk of breast cancer such as early age at menarche, late age at menopause and nulliparity (Hoel 1983, Kelsey 1988,Hayes 1993, Kampert 1988). The increase in mitotic activity within breast tissue is due to circulating levels of estrogens and progestins which are at relatively high levels during the reproductive life of a woman. Thus an increase in the reproductive life span by either an early age of menarche or a late age at menopause increases the total years of mitotic activity of breast tissue and increases the number of potential target cells in the breast susceptible to the effects of a carcinogenic agent such as ionizing radiation (NRC 1990).

After a cancer has been induced in a target cell, the promotion and progression of the cancer appears to be hormonally mediated. Studies on human populations exposed to atomic bomb radiation have shown that women irradiated before 20 years of age are at greater risk of breast cancer than those irradiated later in life (Moolgavkar 1980, Tokunaga 1987, McGregor 1977, NRC 1990). These studies have shown no evidence of excess risk of breast cancer for women who were exposed to atomic bomb radiation after age 40 (Shore 1986, McGregor 1977, NRC 1990,Tokunaga 1994). The results of these studies suggest that radiation induced cancer is hormonally mediated and that the longer the period of exposure to hormonal promoting agents of cancer, the greater the risk of breast cancer.

A latency period of 10 years appears to exist for radiation induced breast cancer. Studies on human populations exposed to atomic bomb radiation show no occurrence of breast cancer in women until age 25 for those women exposed before age 25 (Tokunaga 1987, McGregor 1977, NRC 1990,Tokunaga 1994).

C. Results of Risk Factor Investigations:

The results of investigations of risk factors for breast cancer vary somewhat between studies. Even the results of meta-analyses which attempt to combine the results of primary studies, tend to vary depending on the methods used in the primary studies and those used in the meta-analysis. An excellent summary of the relative risk of breast cancer associated with various factors is provided by Daniel F. Hayes and Stuart J. Schmitt (Hayes 1993).

Those factors which tend to confer a highly elevated risk (relative risk ≥ 4.0) in the female population include age greater than 50 years, country of birth in North America or Northern Europe, a personal history of prior breast cancer, a family history of bilateral, premenopausal breast cancer or family cancer syndrome and atypical proliferative benign breast disease especially with a family history of breast cancer. Those factors which confer a moderate risk of breast cancer (relative risk = 2.0 to 4.0) include any first degree relative with a history of breast cancer, upper socioeconomic status, prolonged uninterrupted menses (e.g. late first pregnancy, nulliparity), postmenopausal obesity, personal history of prior carcinoma of the ovary or endometrium and proliferative benign breast disease without atypia. Those factors which confer a slight risk of breast cancer (relative risk = 1.0 to 2.0) include moderate alcohol intake and menarche before age 12. For oral contraceptive use, hormone replacement therapy and diet, study results have been inconclusive. This could be due to uncontrolled confounding or bias in the studies or may reflect the heterogeneity of the study populations with respect to breast cancer susceptibility.

It is important to identify, eliminate or control sources of bias and confounding to ensure that the results of a study are valid (Hennekens 1987). For investigations of the risk hormone replacement therapy, there are a number of potential sources of bias and confounding that may affect the study results. This includes surveillance bias, selection bias and possible confounding by association of HRT use with other risk factors for breast cancer (Barrett-Conner 1991).

In the next section it will be shown how radiation exposure and long term HRT use have been causally linked with breast cancer. It will also be shown how the use of certain types of controls have resulted in selection bias and reduced the validity or generalizability of the study results.

D. The Risk of Breast Cancer from Ionizing Radiation:

The carcinogenic effect of ionizing radiation has been demonstrated in laboratory studies of animals (Bond 1960, Clifton 1978) and in epidemiologic studies of human populations. An excellent review of these studies can also be found in the BEIR V report of the National Research Council (NRC 1990). In the human population, risk assessment of breast cancer has been conducted on women exposed to ionizing radiation through medical treatment, from atomic bomb radiation and from occupational exposures. Of these populations, the first two have provided the most insight, primarily due to the larger doses of radiation received.

Large breast doses have been received by women treated for tuberculosis through artificial pneumothorax aided by fluoroscopic examination, and by women treated therapeutically with x-rays for benign breast disease, enlarged thymus in infancy, ankylosing spondylitis and cancer. Moderate breast dose has been received during diagnostic examination of women with scoliosis and from film and xeromammography conducted prior to 1985. Since about 1985, lower dose has been received from mammographic exposure, largely due to improved film-screen technology.

A wide range of breast dose was also received by women exposed to atomic bomb radiation. This permitted risk assessment at various dose levels and the development of models for predicting risk at low dose based upon the risk estimates from high dose. Generally, the results obtained from studies of atomic bomb exposure are in good agreement with the results obtained from studies of medical exposure.

Breast cancer incidence appears to increase linearly with radiation dose, have a minimum time between exposure and the appearance of breast cancer (latency period) of about ten years, and to decrease with increasing age at exposure. Women are at greatest risk when exposed early in life especially during the first and second decades of life. Women exposed in the fourth decade of life and beyond are at low risk of breast cancer from ionizing radiation according to most studies.

There does not appear to be any maximum time after exposure that risk disappears and in fact the risk appears to increase in proportion to the natural risk of breast cancer. This has led to the adoption of a relative risk model for breast cancer in which the radiation risk at any given age after exposure is proportional to the natural background risk of breast cancer at that age. Since the natural risk of breast cancer in western women increases with age, the risk of breast cancer from ionizing radiation exposure increases with time from exposure as a multiple of the natural risk. This is in contrast to an earlier and now abandoned model in which radiation risk was thought to be additive with background risk and essentially constant with time after exposure.

One of the earliest studies to suggest a causal association between ionizing radiation exposure and breast cancer was a case series of 50 patients who had been treated for tuberculosis at a sanatorium in Nova Scotia between 1930 and 1952 (Mackensie 1965). 40 of these patients were treated with artificial pneumothorax (lung collapse therapy) and received multiple fluoroscopic examinations as part of their treatment. The fluoroscopic examinations were administered in a fashion which resulted in large x-ray dose to the breast.

The study concluded that irradiation played a significant role in the development of mammary cancer. This conclusion was based upon a positive correlation between the side of the induced pneumothorax and the breast involved with the carcinoma. It was also based on the higher frequency of tumours occurring in the inner half and central breast areas where the x-rays had been focused, compared to the normal situation where tumours usually occur at the upper outer quadrant of the breast. The study also found that women who were irradiated developed breast cancer at a younger age than the normal population of breast cancer patients. Overall, a higher incidence of breast cancer was found in irradiated women (4.8 percent) compared to non-irradiated women (0.17 percent) and a latency period of 8 to 20 years was observed for radiation induced breast cancer.

This study was followed by a number of retrospective studies which also looked at the risk of breast cancer in Canadian women who had been treated for tuberculosis by artificial pneumothorax. Myrden conducted an expanded study of the women used in Mackenzie's study and found 22 breast cancer cases among 300 women who had received fluoroscopic x-rays (7.3 percent) compared to 4 breast cancer cases among 483 women who had not received fluoroscopic x-rays (0.8 percent) (Myrden 1969).

Miller performed a mortality study of 31,710 women treated at 46 Canadian sanatoriums (Miller 1989). In this study, the exposure status of each woman was determined by multiplying the number of fluoroscopic exposures recorded in their medical record by an estimated, average fluoroscopic dose per exposure. The average dose per exposure was determined from thermoluminescent chips placed in a phantom exposed under a variety of fluoroscopic conditions; i.e. patient orientation, shuttered vs unshuttered beam, HVL, etc. (Sherman 1978). The disease status of each patient was determined by linking the patient's medical record to the Canadian National Mortality database.

Women who had received less than 100 mGy dose to the breast were classified as 'unexposed' and women with 100 mGy or more, up to a maximum of 20 Gy, were classified as 'exposed'. The study showed 'exposed women' to have a 36 percent increased risk of breast cancer compared to 'unexposed' women (95 % C.I.; 1.11 - 1.67).

In Miller's study, women were stratified according to age and time since exposure and the relative risk was calculated for each stratum. The relative risk decreased from 4.46 for the youngest exposed group (age 10 to 14 years) to 1.10 for the oldest exposed group (age 35 and older). The relative risk for women age 25 exposed to 1 Gy of radiation, reached its maximal value (RR =1.48) 25 to 34 years after exposure and then decreased. A minimum latency period of 5 years from exposure to the development of breast cancer was observed. The strength of this study toward generalizing the result to North American women, lies in the large number of women included in the study, the fractionation of exposures, and its use of North American women in the cohort. The main limitation of this study is in attempting to generalizing its results to healthy women who are free of tuberculosis since health status may effect susceptibility to breast cancer in unknown ways.

A series of studies were also conducted of women treated for tuberculosis by artificial pneumothorax in Massachusetts sanatoriums from 1925 to 1954 (Boice 1977, Boice 1978, Boice 1981,Davis 1989, Hrubec 1989, Boice 1991). Individual breast dose was determined by Monte Carlo calculations using fluoroscopic data obtained from individual medical records, physician interviews, patient contact and machine exposure measurements.

A recent study of this cohort found strong evidence for a linear relationship between dose and relative risk (Boice 1991). Breast cancer occurred in 147 of the 2,567 exposed women (0.79 Gy average breast dose) and 87 of the 2,367 unexposed women in the cohort. From these results, Boice estimated a relative risk of 1.61 per Gy of breast dose which is comparable to the value of 1.48 per Gy found in the study by Miller.

Boice observed a higher relative risk of breast cancer for younger women than for older women exposed to radiation. However, the relative risk was apparently unaffected by fractionating the dose, and unlike the Canadian study, the relative risk continued to increase with time after exposure. Boice also reported the latency period of breast cancer to decrease with increasing age at exposure and for young women, a minimum latency period of 15 years was observed.

The strength of this study included the careful dose reconstruction that was performed on each individual, the complete follow-up that was carried out, and the highly fractionated nature of the exposures allowing comparison with mammographic exposures. The limitations of the study were its small sample size which reduced the power for subgroup analysis, and the ability to generalize the results to women who are healthy and not suffering from tuberculosis.

Another study involved women who were treated with x-rays for acute post partum mastitis (APM) in Rochester, New York in the 1940s and 1950s (Shore 1986). The study included 601 women with APM who had received 0.6 to 14 Gy of fractionated, therapeutic, radiation dose to the breast and 1,239 women with APM with no radiation exposure. Breast dose was accurately determined for each woman from original radiotherapy records (Cohen 1972) and patient follow-up was performed through mailed questionnaires or telephone interviews to determine disease status that was later verified through pathology reports. Subjects ranged in age from 20 to 40 years old.

The relative risk of 1.40 per Gy found in this study was comparable to the values of 1.48 per Gy and 1.61 per Gy found in the Massachusetts and Canadian fluoroscopy studies respectively . The excess relative risk was found to be a linear function of dose and fractionation of dose did not appear to have any effect on risk as was found in the fluoroscopy studies. Unlike the fluoroscopy studies however, which found a decreasing relative risk with increasing age at exposure, this study found no change in risk with change in age at exposure. Shore attributed this to the increased proliferative state of the lactating breasts of the women in the study.

There was no indication of abscopal radiation effects (i.e systemic effects) from the radiation exposure to account for the increased breast cancer incidence since only the irradiated breasts showed higher incidence of cancer in Shore's study. The latency period for breast cancer was found to be 15 years and was not effected by dose. The temporal pattern of risk was consistent with the relative risk model where radiation risk is proportional to age. The strength of this study included the accuracy of the breast dose determinations and the fractionated pattern of dose allowing comparison with mammographic dose patterns. However, the lactating and inflamed breast condition of the 20 to 40 year old women in this study reduces the ability to generalize the results to women of other ages or breast conditions.

In addition to acute postpartum mastitis, women therapeutically treated with x-rays for other benign breast diseases have been studied. Mattsson performed a retrospective cohort study of 1,216 women in Sweden who were treated with x-ray exposures for either fibroadenomatosis (86%), acute mastitis (9%) or chronic mastitis (5%), between 1925 and 1954 (Mattsson 1993). The breast dose ranged from 3 mGy to 50.1 Gy among these women with a mean dose of 5.8 Gy.

Breast dose was determined by irradiating TLD chips in a phantom under the identical x-ray machine settings (kVp, filtration, focus-skin distance, direction of beam etc.) used in the actual exposures of each woman. Dose to the unirradiated breasts were also determined using tables published in ICRP publication 44 (Protection of Patients in Radiation Therapy) with a range of 3 mGy to 1.18 Gy and a mean dose of 0.27 Gy.

The reference group used for this study was 1,874 Swedish women diagnosed with the same benign breast diseases but who had not received any x-ray treatment. A reference group with benign breast disease was chosen in order to control for the possible confounding effect of benign breast disease on the risk of breast cancer. The age of the irradiated group ranged from 10 to 74 years with a median age of 40 and the age of the reference group age ranged from 10 to 78 years with a median age of 36.

The study found 198 breast cancer cases in the irradiated group and 101 cases in the reference group resulting in a relative risk of breast cancer equal to 3.58 (95% C.I; 2.77 - 4.63). A significant ($P<.001$) dose response gradient was observed ranging from a relative risk of 1.19 for 0.2 Gy to a relative risk of 5.28 for 2.0 Gy. The relative risk was observed to follow a wavelike temporal pattern after exposure, reaching a maximum at 25 years after exposure and then decreasing thereafter. This temporal pattern was also observed in studies of atomic bomb exposures but not in the Massachusetts fluoroscopy studies or the New York APM study.

No significant difference in relative risk was observed from fractionation of exposures. The relative risk was found to decrease with increasing age at exposure, however it was found to be elevated for all age groups including women over the age of 40. Other studies also found radiation risk to decrease with age at exposure but did not find an increased risk for women over the age of 40 (Myrden 1969, Boice 1977, Boice 1978, Boice 1981, Hrubec 1989, Shore 1986, Davis 1989, Miller 1989) . However in the study by Mattsson, a significant dose response gradient was found for older women ranging from a relative risk of 1.6 for 1 Gy to a relative risk of 5.2 for 10 Gy.

The strength of this study lies in the accuracy with which breast dose was determined, the fractionated manner in which exposures were received and the large dose and age range of the study population. The relative risk of 1.6 per Gy for both the treated (high dose) breasts and the untreated breasts (low dose) in irradiated patients agrees well with the relative risk per Gy found in other studies. The relative risk observed in the low dose range and for women over the age of 40 years has particular relevance for women receiving mammographic exposure since it demonstrates a carcinogenic potential of x-rays even at lower doses and in older age groups.

A potential limitation of the study was its ability to generalize the results to women not suffering from benign breast disease if this condition in some way sensitizes the breast to the carcinogenic effects of ionizing radiation. The finding of an elevated radiation risk for women over the age of 40 may be due to the larger number of women over the age of 40 in this study compared to other studies. It may also be due to differences in the populations under study.

In studies of Japanese women exposed to atomic bomb radiation an elevated risk of breast cancer was not found for women over the age of 40. However, a lower degree of hormonal stimulation in older Japanese women compared to western women has been suggested as a possible explanation for this difference in risk (Tokunaga 1987). Postmenopausal Japanese women have a lower incidence of breast cancer than their western counterparts. Since the radiogenic risk of breast cancer is proportional to the natural risk of breast cancer for any given age group, the failure to find an increased risk of breast cancer from radiation exposure among postmenopausal Japanese women would be expected (Tokunaga 1994).

Risk assessment studies have also been conducted for women treated with x-rays for other diseases (Li 1983, Darby 1987, Hildreth 1989, Boice 1989). In a case-control study, Boice found a relative risk of breast cancer of 1.07 in women treated with ionizing radiation for cervical cancer. However, an increased radiation risk of breast cancer was only found for women who had a bilateral ovariectomy before radiation treatment.

The average dose from scatter radiation to the breast in this study was 0.31 Gy and the average age of exposure was 52 years. In the group of women with intact ovaries the relative risk varied with the magnitude of the dose to the ovaries. For an ovarian dose less than 6 Gy the relative risk of breast cancer was 1.12 while for an ovarian dose above 6 Gy the relative risk was 0.65. This indicated a strong protective effect from the cessation of ovarian function. For women without ovaries, radiation exposure to the cervix was not associated with a reduction of ovarian hormones therefore these women were not subject to the confounding effects of loss of ovarian function. The author concluded that for women with bilateral ovariectomies there was evidence of a causal relationship between radiation dose and breast cancer. However they cautioned against over interpretation of the data due to a lack of statistical significance in the dose-response relationship.

This was a good study for assessing the effects of low dose radiation in older women since the natural incidence of breast cancer was low for ovariectomized women allowing radiation induced breast cancer to be more readily detected. The relative risk was elevated for ovariectomized women who received a breast dose exceeding 0.2 Gy but below this dose there was no evidence of an increased risk of breast cancer among any of the subgroups.

In a different study, no increased risk of breast cancer from radiation exposure was found among older women (Storm 1992). 529 women who developed contralateral breast cancer after being treated with adjuvant radiotherapy were compared with matched controls. The mean contralateral breast dose was 2.51 Gy as determined by phantom measurements and the relative risk was found to be 1.04 (95% C.I.; 0.74 - 1.46). There was no evidence that the risk varied with dose, time since exposure or age at exposure and the contralateral breast tumours were evenly distributed (i.e. medial, lateral, central). Since studies of other women found a much greater risk from this level of breast dose, the authors attributed the lower risk to the older age of the women in the study (53% of the women were perimenopausal or postmenopausal). The authors concluded that there is little if any increased risk of radiation-induced breast cancer associated with low-dose radiation from mammography after the age of 45 years.

A difficulty in studies of secondary neoplasms such as the previous two, is in generalizing the results to normal, healthy women with no prior history of breast cancer or other cancers. Coleman has pointed out that genetic predisposition and tumour multiplicity make it difficult to specify the exact risks involved in the development of secondary tumours and in fact some tumours are syndrome related such as secondary osteosarcoma in patients with retinoblastoma (Coleman 1982).

In addition to this, the hormonal influence on the development of breast cancer may be an important factor and studies of women at different stages of hormonal stimulation may give widely different results of risk from radiation exposure. A number of studies have demonstrated the influence of hormone stimulation on radiogenic breast cancer and have suggested that a minimum period of estrogen stimulation is required after radiation exposure (Hoffman 1989, Tokunaga 1994).

Hildreth compared 1,201 women who had received x-ray treatment in infancy for an enlarged thymus with 2,469 non-irradiated women (Hildreth 1989). For an average breast dose of 0.69 Gy the relative risk of breast cancer was 3.6, however the first breast cancer case was not diagnosed until 28 years after irradiation. The study concluded that irradiation of the immature female breast acts as a tumour initiator by altering cells to make them more susceptible to the subsequent tumour-promoting effects of hormones.

In the study of women exposed to atomic bomb radiation, Tokunaga also found that women exposed prior to puberty were at increased risk of breast cancer but not until age 30 (Tokunaga 1987, Tokunaga 1994). The author suggested that the developmental state of breast tissue at the time of irradiation is less important to the subsequent development of radiation induced breast cancer than are events (i.e hormonal) that occur later in life. The finding of a decreased relative risk with increased age at exposure led Tokunaga to suggest that endogenous estrogen was promoting the carcinogenic effect of radiation in prepubescent women and that the younger the age at exposure, the longer the period of endogenous estrogen promotion, and the greater the risk of breast cancer. The BEIR V model for breast cancer also shows the relative risk of breast cancer to decrease with increasing age at exposure (NRC 1990). For a 100 mGy breast dose, BEIR V reports a maximum relative risk of breast cancer equal to 1.55, 1.20, 1.10 and 1.10 for age at exposure equal to 15, 25, 45 and 60 years respectively. 100 mGy is roughly the dose received from 50 mammograms using modern x-ray equipment (Filipow 1997).

In addition to age at exposure, several studies have examined the interaction or synergism between radiation and other non-radiation factors for breast cancer. Boice and Stone found that radiation exposure to the breast during first pregnancy increased the risk of breast cancer (Boice 1978). Shore found a synergistic effect (i.e radiation and the other factor have a multiplicative rather than an additive effect on risk) for irradiation at first pregnancy, but no synergism with family history of breast cancer, late parity, oral contraceptive use or hormone replacement therapy was found (Shore 1980). For oral contraceptive use and for hormone replacement therapy an antagonist effect was observed in which these practices reduced the risk of radiation exposure by a factor of 0.47 and 0.67 respectively. However the authors cautioned against over interpretation of the results since the use of hormones was subsequent to the irradiation and may not apply to the concomitant use of hormones during radiation exposures.

In addition to this the radiation exposures were received by women suffering acute postpartum mastitis who would have been subject to increased hormonal stimulation during lactation. Irradiation at this time could have produced different effects than irradiation of non-lactating or postmenopausal women. Also Shore's study did not take into account the number of years that the irradiation occurred before menopause. The variation in duration of endogenous estrogen stimulation of irradiated breast tissue might influence the risk of breast cancer as much as any subsequent exogenous hormone use.

Recently Goodman analyzed the atomic bomb survivor data for synergism between radiation and other risk factors for breast cancer (Goodman 1997). Women that had used estrogen were found to have a relative risk of 1.64 (1.02,2.64) but no synergism was found between estrogen use and radiation exposure. However the estrogen users in this study would have been premenopausal when exposed to atomic bomb radiation. This would have resulted in endogenous estrogen stimulation of radiogenically initiated cancers in addition to the subsequent stimulation from exogenous estrogen. Neither this, nor the duration of exogenous estrogen use was accounted for in the study.

The risk determined for 'ever use' of estrogen (i.e. estrogen use of any duration) was also significantly higher in this study than in other studies of estrogen use. Most studies of western women have found no elevated risk for 'ever use' of estrogen although some studies have found an elevated risk for long duration estrogen use (Steinberg 1991, Sillero-Arenas 1992, Steinberg 1994). It is possible that atomic bomb radiation may have resulted in a lowering of ovarian estrogen production in exposed

Japanese women conferring a protective effect from breast cancer. The use of exogenous estrogen could have removed this protective effect resulting in the elevated relative risk observed in Goodman's study. However it has been argued that the dose received by most atomic bomb survivors was too small to have resulted in a lowering of ovarian estrogen (Siegel 1966, Boice 1989).

Another possibility is that estrogen treatment is more effective in causing breast cancer in Japanese women than in western women. Tokunaga found that Japanese women who were older than 40 when exposed to atomic bomb radiation did not show any marked increase in risk of breast cancer (Tokunaga 1994). The author suggested that this may be due to lower hormonal stimulation in older Japanese women compared to western women conferring a protective effect amongst Japanese women. The use of estrogen might remove this protective effect resulting in a higher relative risk than what has generally been observed for western women.

These observations underscore the need for caution in generalizing the conclusions drawn from atomic bomb exposures to western women exposed to ionizing radiation. The potential bias caused by genetic differences, or differences in the way exposures were measured could easily account for the differences found in breast cancer risk from radiation exposure or estrogen treatment.

For these reasons, the National Research Council Committee on the Biological Effects of Ionizing Radiation utilized not only the results of the life span study of atomic bomb survivors but also the results of the Canadian and Massachusetts fluoroscopy studies and the New York postpartum mastitis study in modeling the risk of breast cancer from radiation exposure. In the report that came from the study (NRC 1990) the following generalizations were made concerning the radiogenic risk of breast cancer:

1. The development of overt cancer from radiogenically damaged mammary target cells is critically dependent upon the hormonal status of the cells over time.
2. Radiation related breast cancers are similar in age distribution and histopathological types to breast cancer resulting from other known or unknown causes.
3. Women who are irradiated at less than 20 years of age are at a higher relative risk for breast cancer than those who are irradiated later in life.
4. The epidemiologic data reveal little or no decrease in the yield of tumours when the total radiation dose is received in multiple exposures rather than in a single, brief exposure.
5. There is no evidence that the temporal pattern of relative risk is affected by dose or age at exposure.
6. The minimal latency period is probably 10 years since no evidence of elevated risk exists until 10 years after exposure. The latency period is not affected by the magnitude of the dose received, however there is some evidence that younger ages at exposure result in increased latency periods.
7. The risk of breast cancer appears to be a linear function of dose and the use of relative risk is preferred to absolute risk in modeling breast cancer.

E. The Risk of Breast Cancer from HRT:

If the development of breast cancer from radiogenically initiated cells is critically dependent on the hormonal history and environment of those cells, then it is possible that the introduction of exogenous estrogens could affect the risk of breast cancer in irradiated women. The risk of breast cancer from exogenous estrogen or combinations of estrogen and progestin has been extensively studied for different populations of women but not for the subgroup who have received mammographic radiation exposures.

For the general population of women, recent studies and meta-analyses have shown a slightly increased risk of breast cancer for long duration (i.e greater than 10 years) hormone replacement therapy but not for short duration use (10 years or less) or 'ever use' of HRT. However, the results of individual studies and combined studies (meta-analysis) have varied depending on the type of controls used in the study (i.e. community controls vs hospital controls), the type of preparation (e.g, synthetic estrogens, conjugated equine estrogens, estrogen - progestin combinations, estrogen - androgen preparation), the dosage of hormone (1.25 mg, 0.625 mg), and the type of study design employed (i.e. case-control vs cohort).

In a recent meta-analysis, Steinberg et al. found considerable heterogeneity of results between studies using women from different geographical locations and different types of control populations (Steinberg 1994). In particular, studies which used hospital controls tended to find lower relative risks for hormone replacement therapy than studies which used community controls. Steinberg suggested that "many medical conditions are affected by estrogen use and many medical conditions will affect a woman's decision to use estrogen. As a result, estrogen users may not be represented in hospital populations in the same proportion as they are in the community".

Thus the nature of the study population, the specific type of hormone replacement therapy studied and the design of the study itself can affect the outcome of the study and limit the ability to generalize results. In the following paragraphs some of the major epidemiologic studies of hormone replacement therapy are reviewed with attention given to those factors (population type, study design, hormone type, duration, dose , formulation) which may have affected the study results.

Table 1 lists the major epidemiologic studies of HRT and breast cancer that have been conducted since 1976. The table includes 18 cohort studies, 25 case-control studies, 1 clinical trial and 6 meta-analyses for a total of 50 studies. For the purpose of this review, summary relative risk values were obtained from these studies using the method given by Greenland in which the mean relative risk RR_m, of the combined studies was obtained as follows (Greenland 1987):

1. The relative risk for a given exposure duration of the ith study, RR_i, was first converted to the $\ln RR_i$ value.

2. The lnRRi value was then multiplied by a weighting factor, w_i, determined from the confidence interval of the RR_i value where:

$w_i = [3.92 \div \ln RR_{i\text{upper confidence interval}} - \ln RR_{i\text{lower confidence interval}}]^2$ to obtain the value $w_i \ln RR_i$.

3. The sum of the $w_i \ln RR_i$ values, $\Sigma w_i \ln RR_i$, and the sum of the weighting factors, Σw_i, was obtained for the exposure interval of interest.

4. The $\ln RR_m = \Sigma w_i \ln RR_i \div \Sigma w_i$ and the RR_m was obtained from $e^{\ln RRm}$.

5. The confidence interval for RR_m was obtained from $e^{\ln RRm \pm (1.96 \div \Sigma wi)}$.

Figure 1 provides the RR_m of breast cancer from 'ever use' of HRT for studies combined on the basis of study type or control type. From figure 1 it appears that case-control studies and studies using hospital controls have slightly higher RR_m values than cohort studies or studies using community controls. Steinberg suggested that hospital controls might use HRT more frequently than community controls (Steinberg 1994) and found a lower estimated relative risk for hospital control based studies. The results shown here do not support that conclusion, however the large overlap in the confidence intervals makes it difficult to draw any definitive conclusions regarding study type or control type bias.

In addition to bias associated with the type of study or control, there is also potential bias associated with the mode of detection. Horwitz and Stewart studied the effect of different clinical features on the relative risk of estrogen use in a case-control study that included 257 cases and 664 controls (Horwitz 1984). Table 2 summarizes their results.

Based on these results, the authors suggested that the method of diagnosis and the type of control chosen may affect the estimated relative risk and could explain the wide variation in relative risks found in different studies.

The type of replacement hormone used may also influence the risk of breast cancer. There has been considerable controversy over whether treatment by estrogen alone increases the risk of breast cancer or whether estrogen-progestin combinations are required to increase the risk of breast cancer. Table 3 lists various types of hormone preparations that have been used along with the associated mean relative risk estimates obtained by the meta-analytic method described above. From the table it is seen that 'ever use' of conjugated estrogens is not associated with an increased risk of breast cancer whereas 'ever use' of synthetic estrogens is associated with a 21% increased risk of breast cancer that is statistically significant. Conjugated estrogen which is of equine origin, is the predominant replacement estrogen used in North America (e.g Premarin®) while synthetic estrogen (e.g. estriol) is used predominantly in Europe.

Several meta-analyses have calculated the risk of breast cancer for 'ever use' of 'all' estrogens. Dupont estimated the risk to be 1.07 (Dupont 1991), Steinberg estimated 'ever use' risk to be 1.06 (Steinberg 1991) and both results agree well with the risk estimate for 'all' estrogens determined in this study (1.04).

The addition of progestin or androgen to estrogen appears to significantly increase the risk of breast cancer for 'ever use'. However some investigators have argued that the category "ever use" is of little value in providing risk estimates for HRT since it does not adequately address the duration of HRT use (Steinberg 1994).

For this reason summary risk estimates were also calculated for 0 - 9 years and greater than 9 years of HRT use. Again, conjugated estrogens are not associated with an increase in breast cancer risk even after long duration of use whereas synthetic estrogens and estrogens with progestin added show an increase in risk with increasing duration of use which is statistically significant for long term use (> 9 years) of synthetic estrogen. The addition of progestin to estrogen in hormone replacement therapy was not widespread prior to 1985 and the number of studies which have estimated risk from 'long term' use of estrogen-progestin is limited. This in part explains the large confidence interval in the above table for greater than 9 years of estrogen-progestin use.

The effect of HRT regimen and dose had not been extensively investigated prior to the landmark study of menopausal estrogen use by Hoover (Hoover 1976). Hoover found that 'other than daily' use of estrogen was associated with a greater relative risk than 'daily use' of estrogen and that high dosage (> 0.625 mg) was associated with a greater relative risk than low dosage (≤ 0.625 mg). However none of the risk estimates were statistically significant and the effect of dosage and regimen remains uncertain (Brinton 1993).

In addition to the characteristics of hormone treatment, patient characteristics may modify or possibly confound the risk estimates of HRT use. A variety of patient characteristics have been studied using stratified analysis including the type of menopause, race, parity, body mass index, and medical history of the patient.

For type of menopause, three subgroups have been studied including women who have had a natural menopause, women who have undergone a hysterectomy without a bilateral ovariectomy and women who have undergone a hysterectomy with a bilateral ovariectomy. The relative risks determined for these subgroups have varied between studies with some showing an increased risk for women with bilateral ovariectomy (Hoover 1981, Thomas 1982, Wingo 1987, Heinrick 1992), some showing an increased risk for women with intact ovaries (Jick 1980, Ross 1980, Hulka 1982, Kaufman 1984, Ewertz 1988) and others showing no effect between menopausal subgroups (Kelsey 1981, Kaufman 1991, Palmer 1991).

There may be racial differences in the HRT risk of breast cancer which are potentially confounded by cultural characteristics. Nomura found a greater relative risk from HRT use for Japanese residents of Hawaii (RR= 1.2 and 1.9) than for Caucasian residents (RR= .8 and 1.3) using either hospital or community controls (Nomura 1986).

In a meta-analysis, Steinberg found nulliparous women to be at greater relative risk from 'ever use' of HRT (RR = 1.5) than women who had given birth to one or more children (RR = 1.0) (Steinberg 1991). For subgroup analysis based on body mass index (BMI) some studies have found obese women to be at greater relative risk from HRT use than non-obese women (Sherman 1983, La Vecchia 1986, Mills 1989), while other studies have produced the opposite results (Kaufman 1991, Palmer 1991, Harris 1992).

The medical history of the patient or family could also influence the risk of breast cancer from HRT use. For instance, a history of benign breast disease has been found to increase the risk of breast cancer from HRT use in some studies (Ross 1980, Dupont 1991, Steinberg 1991, Brinton 1986, Nomura 1986) but not in others (Hoover 1981, Hulka 1982, Kaufman 1984, La Vecchia 1986, Wingo 1987, Rohan 1988, Kaufman 1991, Palmer 1991). Also a family history of breast cancer has been found to increase the relative risk for HRT use in some studies (Hoover 1981, Hulka 1982, Nomura 1986, Wingo 1987, Kaufman 1991) but not in other studies (Kaufman 1984, Brinton 1986, La Vecchia 1986, Rohan 1988, Mills 1989, Palmer 1991).

Synergism and interactive effects between HRT and other agents such as radiation (Shore 1980, Goodman 1997) oral contraceptives (Mills 1989) and alcohol consumption (Colditz 1990, Gapstur 1992) have been examined with varying results. Ionizing radiation and HRT was not found to interact synergistically in studies conducted by Shore or Goodman, however in both studies most of the women were premenopausal when they received the radiation exposure. In a study by Stanford no effect on HRT risk was seen with increasing number of mammograms received by postmenopausal women although the radiation dose to the breast for each mammogram was not calculated (Stanford 1995).

F. Summary:

In summary, radiation exposure has been shown to be causally linked with the development of breast cancer in persons exposed to atomic bomb radiation and through medical x-ray exposure of the breast. A minimum threshold of radiation dose below which breast cancer does not develop has not been demonstrated. Therefore it is safe to assume that the risk of breast cancer from radiation exposure extends to even low doses of radiation received through mammography.

The best estimate of the excess risk of breast cancer from radiation exposure to the breast is 0.06 per 100 mGy. If this value, which has been determined from high dose studies (> 500 mGy), is also valid for low doses of radiation received through mammography (i.e less than 100 mGy), then the expected relative risk of breast cancer due to mammography would not exceed 1.06.

Relative risk values similar in magnitude to the values predicted for low dose radiation, have been found for 'ever use' of HRT in recent meta-analyses (RR = 1.07, Dupont 1991; RR = 1.06, Steinberg 1991; RR = 1.04, this study). If women who receive hormone treatment also receive regular mammographic exposures, then it is possible that at least part of the elevated risk of breast cancer attributed to HRT use is in fact due to radiation exposure. If an association between HRT use and radiation exposure were demonstrated then it would be important to control for the potential confounding effect of radiation exposure on the estimated relative risk of breast cancer from HRT use. One of the objectives of this study was to determine if this type of confounding was present and to provide controls for it in determining the relative risk of breast cancer from HRT use.

It was also shown that studies of HRT risk may be subject to bias due to selection of specific types of control subjects (Weis 1996). In particular, hospital type controls may be more likely to use HRT than community-based controls resulting in a reduced estimate of the relative risk of breast cancer from HRT use when hospital controls are used (Steinberg 1994). If the unbiased relative risk from 'ever use' is approximately equal to 1.0 then the presence of selection bias in a study would be expected to reduce the estimated relative risk to a value below 1.0. This was observed in the study performed by Horwitz (Horwitz 1984) in which patients from mammography clinics were used as controls and the estimated relative risk of breast cancer from HRT use ranged from 0.4 to 0.9.

Finally, it was shown that hormones may have a significant role in the etiology of breast cancer through the promotion of cancerous lesions induced by ionizing radiation. Evidence for this was found in studies of atomic bomb survivors where the younger the age at exposure the greater the risk of breast cancer for the same radiation dose. Tokunaga suggested that the relationship between risk and age at exposure could be explained by different periods of hormonal stimulation after radiation exposure (Tokunaga 1987).

The second objective of the study was to determine if radiation exposure is an 'effect modifier' of the relative risk of breast cancer from HRT use. 'Effect modification' is different from 'confounding' in that the risk of breast cancer associated with HRT use may vary according to the level of radiation exposure received prior to the HRT use. The next chapter will describe in detail the methods and procedures that were used in this study to determine if the risk of breast cancer is affected by interaction between mammographic radiation exposure and current HRT use.

Chapter 3

Method

A. Introduction:

In this section the research design will be described including a description of the study population, the data sources and data collection procedures, the research design, and the treatment and analysis of the data. A case-control study design was used to estimate the risk of a finding of breast cancer in women who received varying amounts of mammographic radiation exposure and hormone replacement therapy. The study population was obtained from the patient files of a breast imaging clinic (The Lendrum Breast Clinic) that provides diagnostic mammography services and stereotactic needle core biopsies. Cases included women who were positively identified as having breast cancer through histological examination of biopsy samples. Controls included women who were identified as not having breast cancer through histological examination of biopsy samples.

B. Study Population:

The study population shown in figure 2, consisted of postmenopausal women, 60 years of age and older who utilized the services of the study clinic sometime between 1989 and 1998. The study clinic was a diagnostic breast imaging clinic that had 24,420 female patient charts including including 2,110 patients that had been biopsied. From the biopsied group, there were 688 histologically confirmed cases of breast cancer and 1,422 histologically confirmed patients without breast cancer. These represented the potential cases and controls for the study. However, after applying the age and breast cancer history eligibility criteria, only 252 cases and 342 controls remained eligible for the study. From this group, most of the patients were women from Edmonton, Alberta that were referred to the study clinic by a family physician, another clinic or a mammography screening clinic for the purpose of diagnosing a breast condition. Typically, the study clinic received patients experiencing a breast lump, change in size or shape of the breast, breast pain, inversion or discharge from the nipple, ulceration or dimpling of skin on the breast or various other conditions associated with breast cancer. Additionally, patients were received who had a suspicious breast mass, lesion or calcification discovered on a mammogram. The patients were of various races, ages, socioeconomic status, parity, and other characteristics, some of which may have been risk factors for breast cancer. Although some of the patients received by the clinic were male, the vast majority were female.

Upon arriving at the study clinic each patient completed a Patient History form shown in figure 3, to provide information on their date of birth, the location and approximate date of their last mammogram, menstrual history, current symptoms, personal breast history, current medications and family history of breast or other cancers. The study clinic was also provided with additional information from the referral clinic including any previous mammograms that were taken.

Based on this information and information obtained directly at the study clinic, a diagnosis of the patient's breast condition was made by the study clinic radiologist. If breast cancer was suspected, a needle core biopsy was performed and the tissue sample was sent to a pathology laboratory for histological assessment. The pathology report provided information on the type of breast cancer if present, and any conditions that were of a benign nature.

For this study, patients were classified into two categories; biopsied patients with a histological diagnosis of breast cancer and biopsied patients without a finding of breast cancer. Breast cancer patients were classified as either having invasive breast cancer or in situ breast cancer without an invasive component.

Patients were included in the study if they were female, age 60 years or older at diagnosis and their diagnosis was obtained through histological examination of a biopsy sample. The study was limited to women over the age of 60 in order to increase the likelihood that they were postmenopausal at the time of diagnosis since information on age at menopause was not available for the study. The disadvantage of this approach was that it may have increased the potential for confounding in the study. A later age at menopause is a suspected risk factor for breast cancer (Kampert 88, Tricholopolos 72). Since there may also be an association between current HRT use and recent menopause, the HRT users in this study may have had a later age at menopause than the non HRT users. Without knowledge of the patient's age at menopause, or total duration of HRT use, this would result in potential confounding of the risk estimate of breast cancer from HRT use and was a limitation of the study.

Including only biopsied women in the study ensured that the same method was used to diagnose cases and controls so that misclassification bias was minimized. The disadavantage of this approach was that it may have selected patients for the study whose breast condition was associated with a different pattern of HRT use than women in the general population (Steinberg 1994). This could have resulted in a biased estimate of the HRT risk of breast cancer.

Patients were excluded from the study if they had a past personal history of breast cancer prior to the diagnosis at the study clinic. Prior breast cancer is a major risk factor for recurrent breast cancer and may be associated with therapeutic radiation exposure or influence the decision to use replacement hormones (Donegan 1988). Excluding women with prior breast cancer eliminated the potential confounding effect of this factor.

The study did not exclude women on the basis of race or socioeconomic status however, since this information was unavailable. These factors have been associated with a change in risk of breast cancer and may also be associated with different patterns of HRT use (Ownby 1985, Barton 1987, Mettlin 1989). Therefore, the possibility of uncontrolled confounding existed in the study from race or socioeconomic status.

C. Data Sources:

The data collected in this study was obtained from records located in the patient chart including the Patient History form (figure 3), the radiology report (figure 4), the pathology report (figure 5) and mammograms taken at the study clinic or received from the referral clinic. The required information was recorded on a Patient Data Summary Form (PDSF) shown in figure 6 and was specially designed for this study. The following paragraphs describe the records in the patient chart and the type of information collected.

1. Patient History form:

This form was used to collect medical history information from the patient upon their arrival at the study clinic and a copy of the form is shown in figure 3. It includes the patient's name, date of visit, chart number, date of birth, and the location and date of the previous mammogram. It also contains information on the patient's menstrual history including the age at menarche, first day of the last menstrual cycle, the number of pregnancies, the number of live births, how many children were breast fed, and whether or not a hysterectomy or ovariectomy was ever performed. The breast symptoms that the patient was experiencing at the time of the visit were noted including any skin or nipple changes, nipple discharge, breast lumps, pain or discomfort. It contained information on the patient's personal breast history including information on cysts that were drained, recent breast injuries, past breast surgery or breast cancer. It also included the history of any other cancer occurring in the patient or blood relatives.

The Patient History form was designed to assist the radiologist in the examination and diagnosis of the patient's breast condition. Although it contained valuable information for this study, certain information such as race, height and weight, age at menopause, alcohol or tobacco use, country of birth, and socioeconomic status were not included on the form. Therefore it was not possible to identify differences between cases and controls with respect to these factors or to control for any confounding caused by these factors.

In some instances, more than one Patient History form was found in the patient's chart. However, information from the Patient History form was only used if it was obtained prior to the date of the reference pathology report.

The accuracy and reliability of information provided on the Patient History form was difficult to assess except in those instances where the same information was provided more than once (e.g. on the pathology report or referral letter). To increase the reliability of the data, some of the parameters which were presented as continuous variables (e.g HRT duration) in the patient chart were analyzed as discrete variables (e.g. 'ever', 0 months, 1-120 months, > 120 months). This was based on the assumption that patients were more likely to provide an accurate response to 'yes/no' or 'ever/never' type questions than those that required recall of a time or duration.

The validity of information extracted from the Patient History form was evaluated in order to assess the overall validity of the study results. The aspects considered included the construct, content and criterion validity of the information provided. The Patient History form provided the following information used in the study:

Patient sex: The sex of the patient was not explicitly indicated on the Patient History form. It was implicitly provided by other information on the form suggestive of the patient's sex (e.g. menstrual history information) however. This could be verified from the pathology report which explicitly indicated the sex of the patient.

Patient age: Obtained from the D.O.B. on the form. This could be verified by the D.O.B. given on the pathology report. Criterion validity was high for this parameter.

Menopausal status: Obtained from the age of the patient or uterine/ovary status. For women older than 65 years the construct validity was high since this was well above the age range at which menopause occurs. If a hysterectomy or bilateral ovariectomy was indicated on the form this also established the menopausal status of the patient. For women between the age of 60 and 65 who had not received a hysterectomy or bilateral ovariectomy, their menopausal status could not be verified and the assumption that these women were postmenopausal could have been in error. The probability of error was small however since the average age of menopause is 51 years (Donegan 1988).

Prior Breast Cancer: This information was provided under the section entitled 'personal breast history'. The information could generally be corroborated from information given in the pathology report, letter of referral or radiologist report (criterion validity). In addition to this, women who had prior breast cancer were identified at the clinic with a single red tab on their chart. Also an indication of prior breast surgery on the Patient History form supported a claim of prior breast cancer and the content validity of this parameter was high.

Family History of Breast Cancer: This was a close-ended question on the Patient History form (i.e yes, no, unknown). Additional information on the specific members of the family (e.g. mother, sister, daughter) and the age at diagnosis was also requested on the form. When this additional information was provided for reported family breast cancer, it increased the content validity of the response. Since the occurrence of breast cancer among relatives (e.g. mother, sister, daughter) is a risk factor for breast cancer in the patient ,and since it may influence the decision to use replacement hormones, it was treated as a potential confounding factor in this study (Donegan 1988).

Personal History of Benign Breast Disease: The Patient History form contained information on past breast surgery or cysts that were drained in addition to any past breast cancer. Women that gave a negative response to past breast cancer but a positive response to past breast surgery or cysts drained were classified as having a history of benign breast disease. Since benign breast disease is a suspected risk factor for breast cancer and since it may influence the decision to use replacement hormones or to receive additional radiation exposure through mammography, it was treated as a confounding factor in this study (Donegan 1988, Dupont 1989). For patients classified as having had benign breast disease, the type of benign breast disease was not provided on the Patient History form. Therefore for the purpose of controlling potential confounding the construct validity of this classification was reduced in the absence of additional histological information. This is because only some forms of benign breast disease (e.g. atypical hyperplasia) have been shown to confer substantial risk of breast cancer and to have the potential to confound the data analysis with respect to HRT or radiation exposure (Donegan 1988, Kelly 1991, Hayes 1993).

Menstrual History: There are a number of factors related to menstrual history which are suspected as potential risk factors for breast cancer. These include an early age of menarche (i.e. less than 12 years), a late age of menopause (i.e. greater than 55 years), and nulliparity (Donegan 1988, Stoll 1989, Kelly 1991, Hayes 1993). It has also been suggested that the type of menopause (i.e. natural or surgical) may effect the risk of breast cancer although the association is not as strong as some of the other menstrual factors mentioned (Hayes 1993). In this study, information was collected on the age of menarche, parity and type of menopause of each patient. Information on the age of menopause was not available however and the potential confounding effect of this factor could not be controlled in this study. The Patient History form provided information on the number of live births and since nulliparity is a suspected risk factor for breast cancer its potential for confounding was also considered in the study (Hayes 1993). The type of menopause was also recorded in terms of the presence or absence of a hysterectomy or ovariectomy. It has been suggested that a bilateral ovariectomy reduces the risk of breast cancer but at the the same time may increase the likelihood of a women using replacement hormones (Kelly 1991). For this reason it was considered for its potential to cause negative confounding on the HRT risk of breast cancer. The content validity of information on parity and hysterectomy was increased by a number of questions that were related to each of these characteristics. This may not have been the case for information on ovariectomy status since some women may not have known whether they received a unilateral or a bilateral ovariectomy.

History of Cancer other than Breast Cancer: The history of cancer other than breast cancer was also provided on the Patient History form for both the patient's immediate relatives and for the patient's themselves. This information was important since breast cancer may be associated with the occurrence of other types of cancer and this in turn may influence the decision to use replacement hormones or have regular mammograms taken (Vorherr 1980, Barrett-Connor 1991, Weis 1996). The construct validity of this classification depended upon the specificity of the information provided since certain types of cancers (e.g. ovarian) are more strongly associated with breast cancer than others (Lynch 1989).

Hormone Replacement Therapy: The Patient History form contained information on HRT including the type of hormone and duration of current use. However it did not provide any information on the dose, regimen, or method of administration of HRT and it did not account for any hormone replacement therapy that was discontinued. This later information was particularly problematic for the study especially if the risk of breast cancer from HRT use depends on the cumulative duration of past HRT use. Some studies have found that duration of any past use, especially long duration use, is a risk factor for breast cancer (Palmer 1991, Brinton 1986). Other studies have found that the duration of current use is the important factor in determining risk from HRT use (Colditz 1995, Mills 1989). Since it was possible that some women who were not currently using HRT, had some unreported past use of HRT, the possibility for misclassification bias existed in the study with respect to HRT usage.

Therefore each patient was classified as either currently using HRT or not using HRT without consideration of the duration of past use. The validity of classifying patients in this manner depended on the accuracy of the information provided by the patient on current drug use. It was difficult to assess the validity of classifying a patient as an HRT user or nonuser based solely on information from a questionnaire. It was even more difficult to assess the validity of classifying a patient as a nonuser when they did not respond to the question of HRT use on the Patient History form. When patients provided information on the duration of current usage it increased the content validity of classifying them as an HRT user.

Given these limitations the most straightforward and valid analysis was one based on a discrete classification of current HRT use in which patients were classified as either current HRT users, non HRT users or had unknown current HRT status. The latter category represented 5.6 percent of the 342 controls and 12.7 percent of the 252 cases in the study.

Other Prescription Medication Taken: The Patient History form contained information on other prescription medication that was currently used by the patient. This information was collected for the purpose of identifying any drug use bias between cases and controls in the study. Other prescription medication use was recorded as either yes, no, or no response without specifying the type of medication used.

Mammographic Radiation: An objective of the study was to determine if mammographic radiation exposure modified or confounded the estimation of the risk of breast cancer from HRT use. Therefore the cumulative breast dose of each patient was determined from information recorded on the Patient History form and from the mammographic films found in the patient charts. The Patient History form only provided information on the date and location of the previous mammogram. If the previous mammogram was received at a location other than the study clinic, a copy of the mammographic film might be found in the patient chart. If not, the dose from that exposure could not be determined directly and was estimated by an approximation method given in Appendix A.

Two methods were used to determine the average glandular dose from mammographic radiation exposures. The first method involved a calculation of the breast dose based on x-ray machine parameters including the voltage (kVp), milliampere-seconds (mAs) and patient compressed breast thickness (CBT) (Wu 1991, Bushberg 1994). Generally this information could be found on the x-ray film itself and the method of calculating average glandular dose (AGD) from these parameters is given in Appendix A. When CBT information was not provided on an x-ray film the CBT value that was used was the average of all CBT values from other x-ray films for the patient. When none of the x-ray films in a patient's chart provided CBT information, a nominal value of 4.5 cm was used to calculate breast dose based on a recent North American survey of mammography patients (Gentry 1996).

When mAs or kVp information was missing for a given mammographic exposure, the method that was used to calculate AGD was to approximate the dose using a graph of mrad vs CBT shown in Figure 7 (Gentry 1996). This method was used for either x-ray films that did not have mAs or kVp values stamped on them or for known mammographic exposures in which the x-ray film was unavailable.

2. The Radiology Report:

The radiology report shown in figure 4 summarized the mammographic findings of the radiologist including any abnormalities, breast masses, or calcifications that were found as well as the indications for the biopsy. It also provided breast history information related to past cancers or mastectomies that were performed. In this respect it helped eliminate patients from the study who had a history of breast cancer prior to the latest diagnosis. It also served to validate reports of prior breast cancer obtained from the Patient History form.

3. The Pathology Report:

For each patient that received a biopsy, a report from the pathology laboratory was found in the patient's chart providing information on the histological characteristics of the tissue sample (figure 5). In some instances, more than one pathology report was found in the patient chart. If a diagnosis of breast cancer was made on more than one pathology report, the earliest pathology report to indicate breast cancer in the patient was used as the reference report. If none of the pathology reports indicated a finding of breast cancer, the most recent report was used as the reference. The pathology report that was used in the study is referred to as the 'reference pathology report'.

The reference pathology report provided information on the patient's name, age, and sex and was compared to the information provided on the Patient History form to verify the identity of the biopsy sample, the sex of the patient and the age of the patient at the time of biopsy. The latter information was used to exclude patients who were under the age of 60 years at the time of biopsy. The histological characteristics which were of interest to this study and which were extracted from the pathology report included the breast side, type of disease, stage of breast cancer and tumour size. Breast side was a nominal variable recorded as either right or left. In some cases both breast sides were involved and data on each side was recorded separately. The type of disease was a nominal variable and was recorded as either invasive breast cancer, in situ breast cancer, or benign. In some cases both invasive and in situ components were identified in a given breast tissue sample. Samples were classified as benign only if no invasive or in situ components were found. The stage of breast cancer was applicable only to patients with invasive disease and was classified as stage I (no lymphatic involvement) and stage II (lymphatic involvement) (Vorherr 1980). The tumour size identified in the reference pathology report was a continuous variable and was recorded in this study to the nearest tenth of a centimeter.

Information extracted from the pathology report was expected to have a high degree of validity with respect to disease classification with virtually no false positives (i.e misclassified cases) (Rosen 1978). False negative results (i.e. misclassified controls) are a more common occurrence with estimates of 7-20% for clinical examination, 12-16 % for mammography and approximately 5% for biopsy with histological examination (Rosen 1978). The majority of false negatives for histological examination involve non-invasive ductal carcinoma in situ or biopsy samples that fail to capture an existing neoplasm (Rosen 1978, Zhou 1989). Misclassifying controls with respect to disease status should not affect the estimate of risk associated with exposure to HRT provided that the misclassification of disease is not related to the HRT use (Hennekens 1987). The tumour size was reported to the nearest tenth of a centimeter in the pathology report. Classification of breast cancer stage was based on a finding of either no lymphatic involvement (stage I) or lymphatic involvement (stage II). The accuracy of this information was expected to be high since it was a routine parameter identified in the pathology report.

Overall the information extracted from the reference pathology report is credited with a high degree of validity. Since the pathologist was unaware of exposures that the patient had received (replacement hormones and radiation), any misclassification of disease should not have been related to these exposures. The radiologist however, was aware of HRT use that the patient reported on the Patient History form. While this could have affected the decision to perform a biopsy, it would not have resulted in selection bias between cases and control since both of these groups were biopsied.

4. Mammograms:

The mammographic films found in the patient chart provided information for calculating the average glandular dose (AGD) received by the patient. This included information on the peak kilovoltage (kVp) and milliampere-seconds (mAs) of the exposure as well as the compressed breast thickness (CBT) of the patient during the exposure. The accuracy of the information provided on each of these parameters depended on the calibration of the x-ray equipment. Since quality control checks were routinely performed on mammographic equipment, the accuracy and reliability of the x-ray machine data was generally maintained at a high level (Filipow 1997). However errors that occurred in recorded kVp, mAs and CBT value could have resulted in errors in the calculation of AGD. Assuming a worse case scenario of ± 0.5 kVp, ± 5 mAs and ± 0.5 cm CBT this would result in a 31 percent error in the estimation of AGD as shown in Appendix A. When x-ray machine data was unavailable for a recorded exposure, the AGD was estimated by the approximation method given in Appendix A. In this method, average glandular dose was obtained from a graph of mrad versus CBT shown figure 7 (Gentry 1996). The average CBT value used in determining average glandular dose was obtained from mammographic films found in the patient chart. The error in the AGD value obtained by this method may be 50 percent or more for any given exposure (Gentry 1996). However for most patients, there were relatively few exposures that relied on this method for the determination of AGD and the overall error in the calculated value of lifetime AGD probably did not exceed 30 percent as shown in Appendix A.

5. The Patient Data Summary Form:

The Patient Data Summary Form (PDSF) shown in figure 6 consists of information on patient characteristics, disease status, medical history and exposures of interest that were extracted from records in the patient chart. The PDSF contains 31 parameters including patient identification, patient demographics, cancer history, benign breast disease history and breast symptoms, diagnostic information, current HRT use and mammographic radiation exposure history. The information collected from parameters 16 through 31 on the PDSF was specific to the right or left breast. This was important for comparing disease information with the radiation exposure history of each breast.

The data collection instructions for completing the PDSF can be found in Appendix B. These instructions were designed to provide detailed guidelines for collecting information from the patient chart and recording it on the PDSF for later analysis. The purpose of the data collection instructions was to minimize error and bias in collecting data . It was not practical to 'blind' the investigator with respect to the disease status of the study subjects during data collection. Therefore a strict protocol was followed to ensure that data collection was carried out in an identical fashion for all cases and controls.

Information was collected on breast disease, potential confounding factors, exposures of interest and data required to select patients for the study. The information collected was based on the analytical requirements of the study and the type of information collected in similar studies. It was limited by what was available to the investigator from the patient files since no follow-up interviews or patients tests were conducted by the investigator. Data was generally collected as it was recorded in the patient chart however some parameters which were originally recorded as continuous variables were later grouped into discrete categories for analysis. This approach simplified certain portions of the analysis and helped preserve the validity of the data when the accuracy of the information was in question.

D. Data Collection Procedures:

1. Identification and Selection of Study Subjects:

Patients were selected for the study if they were women of age 60 years or older at the time of diagnosis and the diagnosis was performed by histological examination of a biopsy sample. Patients who received a biopsy at the study clinic were identified by a green colored tab placed on the outside of their chart which provided a visual aid for identifying these patients. The patient's sex was determined from information provided on the reference pathology report to exclude male patients from the study. The patient's age at diagnosis was determined from the reference pathology report and verified by subtracting the patient's date of birth from the date of the reference pathology report. Patient age was recorded on the Patient Data Summary Form in years and months. Patients with a past personal history of breast cancer were identified and excluded from the study when this information was indicated on the pathology report, the radiology report or the Patient History form.

2. Completion of the Patient Data Summary Form:

The Patient Data Summary Form (PDSF) shown in figure 6 was used to record information from the patient records using the instructions given in Appendix B. If information on a particular parameter was unavailable or unknown, this was noted on the PDSF. The following paragraphs summarize the data that was collected and provide a brief description of the significance of each parameter for the study.

PDSF sequence number: A sequential number was assigned to the PDSF beginning with 0001 for the first study subject.

Patient chart number: The chart number was recorded on the PDSF as the primary identifier of the study subject.

Patient sex: The sex of the patient was identified from the pathology report and was used to exclude male patients from the study.

Patient date-of-birth: The patient's date-of-birth was identified from the reference pathology report and was recorded as the year and month of birth. It was used in calculating the patient's age at diagnosis.

Parity status: The number of pregnancies that resulted in live births were identified from the Patient History form and was recorded as an integer. Nulliparity was important to the study as a potential confounding factor.

Age at menarche: The age at first mensus was identified from the Patient History form and was recorded to the nearest whole integer on the PDSF as a potential risk factor for breast cancer.

Hysterectomy status: The hysterectomy status of the patient was determined from the Patient History form and was recorded as either 'yes' or 'no' on the PDSF. Since there may be a difference in breast cancer risk among women who have had a hysterectomy accompanied by a bilateral ovariectomy and since HRT use may be more common among hysterectomized women, this was a potential confounding factor that was controlled in study.

Ovariectomy status: The ovariectomy status of the patient was determined from the Patient History form and recorded as either 'bilateral', 'unilateral' or 'none'. Related to but separate from hysterectomy status, it is a potential confounding factor.

Past personal cancer: The presence of a past personal cancer in the patient was determined by reviewing all of the records available in the patient chart especially the Patient History form. If no past personal cancer was identified, 'none' was recorded on the PDSF. If past personal cancer was identified the type of cancer was recorded on the PDSF. Patients with a past personal breast cancer history were excluded from the study since prior breast cancer has a high potential for confounding the study results.

Family cancer history: A family history of cancer was determined by reviewing all of the records available in the patient chart especially the Patient History form. If there was no family history of cancer, 'none' was recorded on the PDSF. If there was a family history of cancer the type of cancer was recorded on the PDSF. This was a potential confounding factor for the study since there may be a difference in breast cancer risk and HRT use or mammographic utilization among women with a family history of cancer.

Information was collected separately for the right and left breast on the following parameters:

Benign breast disease: A history of benign breast disease was identified from information given on the Patient History form. If cysts were drained or breast surgery was noted without the presence of breast cancer then 'yes' was recorded on the PDSF. If there was no indication of past benign breast disease, 'none' was recorded on the PDSF. There may be a different risk of breast cancer and HRT use among women with a history of benign breast disease and this was considered a potential confounding factor for the study.

Current breast symptoms: Breast symptoms prior to diagnosis were identified on the Patient History form as either skin or nipple changes, nipple discharge, pain or discomfort, or breast lumps. If any of these symptoms were noted, 'yes' was recorded on the PDSF. If no symptoms were noted, 'none' was indicated on the PDSF.

Duration of breast symptoms: In addition to identifying the presence of breast symptoms, the duration of breast symptoms was also indicated on the Patient History form. This was recorded on the PDSF as a continuous variable in units of months.

Patient Age at Biopsy: The patient's age at the time of biopsy was determined from the reference pathology report and verified by subtracting the year/month of the patient's date-of-birth from the year/month of the reference pathology report. This information was used to exclude women who were less than 60 years of age at biopsy.

Diagnosis: The diagnosis of the patient with respect to breast cancer was determined from the reference pathology report and was recorded on the PDSF as invasive breast cancer, in situ breast cancer without an invasive component or as a benign condition without the presence of breast cancer. This information was then recorded on the PDSF.

Tumour size: The breast tumour size of patients classified as having invasive or in situ breast cancer was found in the reference pathology report and recorded on the PDSF to the nearest millimeter. Where more than one tumour was reported, the largest tumour was the one recorded on the PDSF. Information on tumour size was collected in order to determine if HRT use had an effect on the size of tumours detected in breast cancer patients in this study.

Stage of breast cancer: The stage of breast cancer for each case was determined from information in the reference pathology report. Stage I was defined as the presence of invasive breast cancer without evidence of spread to the lymphatic system (i.e lymph nodes). Stage II was defined as the presence of breast cancer with evidence of lymphatic involvement. Cases were therefore classified as either stage I or stage II. Patients with more advanced breast cancer than stage II were also classified as stage II since the primary objective of collecting this information was to determine if HRT use affected the progression of breast cancer from stage I to stage II.

Current HRT use: Current use of HRT by patients was determined from information provided on the Patient History form. 'Yes' was recorded on the PDSF if the patient was currently using HRT and 'no' was recorded on the PDSF if the patient was not currently using HRT.

HRT type: For patients with current HRT use, the type of HRT was recorded on the PDSF from the information provided on the Patient History form. The type of HRT used was recorded as either estrogen, progestin or a combination of estrogen and progestin. Risk analyses was conducted for each type of HRT used.

HRT duration: For patients with current HRT use, the number of months of HRT use was recorded on the PDSF from the information provided on the Patient History form. Risk analyses was conducted for different durations of current HRT use.

Other medication use: The use of prescription medication other than HRT was indicated on the Patient History form and was recorded on the PDSF as 'yes' or 'no'. This information was collected for the purpose of identifying drug use bias between cases and controls.

Location of mammogram: The location in which a mammogram was taken was stamped on the mammographic film or was indicated on the Patient History form. This information was recorded on the PDSF as either 'study clinic', or 'other clinic' if the mammogram was received outside of the study clinic. This information was important since a different method was used to determine breast dose for mammograms received at the study clinic than for those received outside of the study clinic. These methods are described in Appendix A.

Date of mammogram: The date that the mammogram was received was stamped on the mammographic film or indicated on the Patient History form. This information was recorded on the PDSF as the year/month in which the mammogram was received. It was used to exclude mammographic exposures that were received less than one year from the date of the reference pathology report which were assumed to be of no biological significance (NRC 1990).

Mammogram kVp: The kVp of a mammogram was generally stamped on the mammographic film and was recorded on the PDSF to the nearest tenth of a kilovolt.

This information was used to calculate mammographic dose by the calculation method outlined in Appendix A.

Mammogram mAs: The mAs of a mammogram was generally stamped on the mammographic film and was recorded on the PDSF to the nearest mAs. This information was used to calculate mammographic dose by the calculation method outlined in Appendix A.

Mammogram CBT: The CBT of a mammogram was generally stamped on the mammographic film and was recorded on the PDSF to the nearest millimeter. When CBT information for a specific mammogram was unavailable, the average CBT value calculated from previous mammograms was recorded on the PDSF for that mammogram. This information was used by both dose estimation methods outlined in Appendix A.

Average glandular dose (AGD): The AGD received from a mammogram was estimated by one of the two methods outlined in Appendix A and recorded on the PDSF to the nearest mrad. Figures 7 was used to estimate AGD by the approximation method and figures 8 and 9 were used to estimate AGD by the calculation method.

Figure 7 was obtained from a study in which the average glandular breast dose was determined for 4,400 women of varing compressed breast thickness, from 170 clinics located in the United States, between 1993 and 1994 (Gentry 1996). The average glandular dose for each woman was determined by measuring skin entrance exposure using TLD chips which was converted to average glandular dose using published D_{gn} values (Wu 1991). For a given compressed breast thickness, breast doses from the 170 facilities were averaged and plotted as shown in figure 7.

Figure 8 was obtained during quality assurance testing of the mammographic unit found at the study clinic (Filipow 1997). Figure 9 was derived from values obtained by

Monte Carlo calculations, performed in a study by Wu et al., for breasts of 100% adipose tissue (Wu 1991).

Cumulative Breast Dose: The cumulative breast dose was calculated by summing the individual AGD values that were received more than one year from the date of the reference pathology report. This information was recorded on the PDSF to the nearest mrad value.

E. Research Design:

1. Introduction:

The objective of this study was to determine if mammographic radiation exposure interacts with replacement hormones to modify the risk of breast cancer among postmenopausal women having biopsies for suspected breast abnormalities. To make this determination, a case-control study was carried out and separate odds ratios calculated for women with different histories of mammographic exposure and HRT use. The women chosen for the study were patients that had undergone a breast biopsy at the study clinic. The study was retrospective in that all patients were diagnosed sometime between 1989 and 1998 prior to the commencement of the study. Furthermore, only HRT and radiation exposures that occurred prior to the date of the reference pathology report were considered. For HRT this included all current use up to the date of the reference pathology report and for radiation exposure it included all exposures up to 12 months prior to the date of the reference pathology report.

2. Study Design Rationale:

A case-control design was chosen for this study so that it could be conducted within a relatively short period of time using a sample of moderate size from the study population and involve minimal expense. All of the data on HRT and radiation exposure, disease status and other characteristics of the patients were obtained solely from information found in the patient charts at the study clinic. This allowed the data to be collected immediately once a data collection protocol was developed. This portion of the study took approximately four months to complete.

3. The Study Population:

Figure 2 shows the population of patients which were available for the study. 24,420 female patients had been seen at the study clinic between 1989 and 1998 and from this group, 2,110 women had undergone a breast biopsy for breast cancer. 688 of these women were diagnosed with either invasive or in situ breast cancer and they represented the potential cases for the study. The remaining 1,422 women were diagnosed free of breast cancer and they represented the potential controls for the study. To be eligible for the study, women had to be 60 years of age or older with no diagnosis of breast cancer prior to the date of the reference pathology report. This reduced the number of eligible cases to 215 with invasive breast cancer and 37 with in situ breast cancer but no invasive component. It reduced the number of eligible controls to 342.

4. The Main Outcome Measure:

The main outcome measure of the study was the relative risk of breast cancer from current hormone replacement use and radiation exposure as estimated by the odds ratio. The definition of the odds ratio is given in Chapter 1. In the context of this study it refers to the ratio of the odds that cases were exposed to an agent of interest to the odds that controls were exposed to the same agent. The odds ratio was estimated by two different methods in this study. The first method involved the use of a contingency table as illustrated in table 4. In this table the values a and b are the respective number of cases and controls exposed to the agent of interest and the values c and d are the respective number of cases and controls not exposed to the agent of interest. The measure of the risk of developing breast cancer from the agent of interest is the odds ratio which is determined from the following expression:

$$\text{Odds Ratio} = (a/c) \div (b/d) = ad \div bc$$

A 95 percent confidence interval for the odds ratio was calculated using the following expressions:

$$\text{Standard Error} = \text{S.E.} = (1/a + 1/b + 1/c + 1/d)^{1/2}$$

$$\text{Confidence Interval} = e^{\ln(\text{odds ratio}) \pm 1.96\ \text{S.E.}}$$

The second method for determining the odds ratio, and the one preferred in this study, was to perform a logistic regression analysis of the data. Logistic regression is based on the relationship:

$$\text{odds}\ (m) = \exp\ (\beta_0 + \beta_1 m) \quad \text{and} \quad \text{odds}\ (n) = \exp\ (\beta_0 + \beta_1 n)$$

where odds (m) is the odds of disease occurring at level m exposure and odds (n) is the odds of disease occurring at level n exposure and β_1 is the risk coefficient. Therefore;

$$\text{odds ratio} = \exp\ (\beta_0 + \beta_1 m - \beta_0 - \beta_1 n) = \exp\ \beta_1(m - n)$$

In the case where m and n are dichotomous variables with values of 1 and 0 respectively (i.e exposure vs no exposure) the odds ratio is equal to exp (β_1).

Logistic regression was used to simultaneously control for a variety of potential confounding factors such as patient age at diagnosis and history of benign breast disease. Although stratified contingency table analysis can also control for confounding, it was impractical to use this method to control for more than a few confounding factors at a time therefore logistic regression was the primary technique used to obtain odds ratios in this study. A complete discussion of logistic regression analysis is given in the text by Hosmer and Lemeshow (Hosmer 1989) and its application is described in the SPSS Advanced Statistic User Manual (SPSS 6.1, 1994).

5. Sample Size Requirements:

The sample size required for a case-control study depends on the level of statistical power and confidence desired in the study but also on the proportion of controls exposed to the factor of interest and the anticipated odds ratio (Hennekens 1987). The general formula used for case-control studies is:

$$n \text{ (each group)} = (p_0 q_0 + p_1 q_1)(Z_{1-a/2} + Z_{1-b})^2 / (p_1 - p_0)^2$$

where: p_0 = proportion of exposure among the controls

= 0.3 (preliminary estimate based on random sample)

$q_0 = 1 - p_0 = 0.7$

p_1= proportion of exposure among the cases

= p_0 x odds ratio detectable

= 0.3 x 1.5

= 0.45

$q_1 = 1 - p_1 = 0.55$

$Z_{1-a/2} = 1.96$ (2-sided test at p = .05)

$Z_{1-b} = 0.84$ (for 80% power of detection)

Substituting these values into the general formula gives:

$$n \text{ (each group)} = \frac{[(.3)(.7) + (.45)(.55)](1.96 + .84)^2}{(.45 - .3)^2}$$

$$n \text{ (each group)} = 159$$

Therefore 159 cases and 159 controls were required for the study in order to detect an odds ratio of breast cancer associated with HRT use of 1.5 or greater with 95 percent confidence and 80 percent power of detection. An odds ratio of 1.5 is within the range of values found for HRT studies of this type and since the number of invasive breast cancer cases (215) and controls (342) eligible for the study exceeded the required sample size, the study was deemed to be justified on statistical grounds.

F. Research Hypothesis:

The research hypothesis for this study was given in chapter 1 and is restated here. It is hypothesized that the odds ratio of breast cancer from mammographic radiation exposure is modified by the duration of current HRT use.

$$H_0: OR_x = OR_y \qquad \text{vs} \qquad H_1: OR_x \neq OR_y$$

Where OR_x equals the odds ratio of breast cancer from mammographic radiation exposure and current HRT use of duration x and OR_y equals the odds ratio of breast cancer from mammographic radiation exposure and current HRT use of duration y. It is also hypothesized that the odds ratio of breast cancer from hormone replacement therapy (HRT) is modified by radiation exposure received from mammography.

$$H_0: OR_n = OR_m \qquad \text{vs} \qquad H_1: OR_n \neq OR_m$$

Where OR_n equals the odds ratio of breast cancer from current HRT use and mammographic dose of level n and OR_m equals the odds ratio of breast cancer from current HRT use and mammographic dose of level m.

G. Treatment of the Data:

Data on patient characteristics, disease status, HRT use and radiation exposure was recorded on the Patient Data Summary Form (PDSF) shown in figure 6 from the information found in the patient charts at the study clinic. This information was entered into the database of a statistical software program (SPSS 6.1, 1994) consisting of 21 fields which corresponded to the parameters listed on the PDSF.

The SPSS program was used to obtain summary information of patient characteristics, determine odds ratios and associated confidence intervals, and to perform tests of statistical significance. Although odds ratios and confidence intervals can also be estimated by cross tabulating the data and using standard formulas, the preferred method in this study was logistic regression which provided better control over potential confounding factors.

In logistic regression, the significance of a risk factor can be determined by examination of the confidence interval around the odds ratio, by determination of the Wald statistic, or by performing a log-likelihood ratio test (Hosmer 1989). In this study all three methods were used.

The confidence interval around the odds ratio is a function of sample size. When it includes the value 1.0 the null hypothesis cannot be rejected and the odds ratio for the risk factor is not statistically significant.

The Wald statistic is equal to the risk factor coefficient β divided by the standard error of β, quantity squared . The Wald statistic follows a standard normal distribution and when its associated p value for a two-tailed test is less than 0.05, the null hypothesis of β equal to zero is rejected.

Occasionally when the standard error of β is large, the Wald statistic fails to reject the null hypothesis even when the risk coefficient is significant (Hosmer 1989). Therefore the log-likelihood ratio test was also used to test the significance of terms in the logistic regression model. The log-likelihood ratio test statistic G is determined by subtracting the log-likelihood for the logistic regression model that includes the term to be tested, from the log-likelihood of the same model which does not include the term. The difference in the log-likelihood values follows a chi-square distribution and when the associated p value is less than 0.05 there is strong evidence that the term is a significant variable in the model.

The objective of this study was to determine if mammographic radiation dose and current HRT use interact in affecting the risk of breast cancer. To do this, a logistic regression model was developed to determine if a significant interaction term between HRT use and radiation dose existed in a multivariate risk model of breast cancer. This multivariate model ncluded other breast cancer risk factors found to be either significant or biologically important in the study population.

A univariate logistic regression was first carried out for each variable. Then for screening purposes, variables were selected if the p value associated with the Wald statistic was less than 0.25. A multivariate logistic regression fit of the selected variables was then performed and the significance of each term in the model was determined by the log-likelihood ratio test.

After identifying the main risk factors of breast cancer, interaction between the individual risk factors was investigated. Interaction terms were added one at a time to the main effects model and after each addition, the log-likelihood ratio test performed to determine the significance of each interaction term.

From these tests a revised multivariate logistic regression model was constructed consisting of individual variables or interaction terms which were statistically significant ($p < 0.05$) as well as any factors that might confound the risk estimate of HRT or radiation dose. For the final logistic regression model, odds ratios were calculated for the variables of interests to allow interpretation of the model.

In addition to logistic regression, a stratified analysis was also carried out on certain subgroups of data. By creating contingency tables of disease versus exposure, odds ratios were calculated using the relationship, odds ratio = ad / bc. To test the null hypothesis that the stratum-specific odds ratios were equal, the Mantel Haenszel chi-square test of homogeneity with one degree of freedom was performed.The stratum-specific odds ratios were considered to be significantly different if the value of chi-square was greater than or equal to 3.841.

H. Limitations of the Study:

There are a number of factors which have the potential to reduce or limit the validity or generalizability of the study results. These include factors which can bias the study results, confound the relationship between the exposure and disease of interest, or reduce the statistical significance of the study results. The following paragraphs describe those features of the study sample, data collection, and research design which may have limited the validity or generalizability of the study results.

1. Sample Limitations:

A major factor in case-control studies which tends to reduce the generalizability of the study results is the type of control group used. In order to maintain a high degree of generalizability the controls should be representative of the general population with respect to the exposure of interest. In this study, the controls were women seeking medical attention for benign breast conditions. It is possible that in some instances the breast conditions were caused by HRT use. It is also possible that the study controls represented a subgroup with greater access or tendency to use medical services and prescription medication than the general population. In either event this would have resulted in a biased lowering of the estimated relative risk of breast cancer from HRT use. In spite of the inherent limitations in using hospital controls they were used in order to preserve the internal validity of the study results. Since the controls were diagnosed using the same set of histological criteria as the cases the chances of differential misclassification of controls was reduced. Another concern was surveillance bias in which patients might have received more intense or rigorous examination based on their history of HRT exposure. By ensuring that cases and controls were diagnosed using the same set of criteria, surveillance bias was minimized in the study.

2. Research Design Limitations:

In addition to the limitation of using hospital controls, several other limitations are inherent in case-control studies. The most important of which is the ability to obtain complete and accurate information on exposures of interest. In this study information on current HRT use and mammographic radiation exposure was obtained exclusively from records in the patient chart. These records were designed primarily for clinical purposes which left certain research questions unanswered. For instance, there was no information available on HRT dose or regimen for individual patients nor was there any information on HRT use that had been discontinued. The study could only estimate the risk of breast cancer from 'current' HRT use although information was available on both the type and the duration of current HRT use.

With respect to radiation exposure, there was a lack of information on mammographic exposures received outside of the study clinic except for the most recent exposures. It was therefore necessary to limit the analysis to patients who only received radiation exposures within the study clinic unless all outside exposures could be identified. This reduced the number of patients available for analysis and the statistical power of the study.

The issue of recall bias was eliminated from this study by only using information on HRT exposure obtained from the Patient History form. This form was completed by all patients prior to their diagnosis at the study clinic. Since breast cancer status was determined after patients had provided HRT information, it is unlikely that selective recall of HRT use would have occurred between cases and controls based on an awareness of disease status.

The disadvantage of only using the Patient History form for certain information such as HRT use, was that the accuracy of the information could not be easily verified. Without access to medical records located outside of the study clinic or information obtained through follow-up interviews, much of the data collected in the study could not be validated. However, parameters which were recorded as dichotomous variables were less of a concern in this respect than continuous variables. For example, the response to a close-ended, 'yes' or 'no' question on current HRT use, was probably more accurately given than the response to a question on the duration of HRT use. Although the accuracy of information provided on the Patient History form could not be verified, there was no reason to suspect any difference in accuracy between cases and controls. This conclusion was based on a similar distribution of certain characteristics such as 'age at biopsy' between cases and controls. Therefore, random misclassification of HRT status in cases and controls more likely affected the magnitude rather than the direction of the estimated relative risk of breast cancer.

Another concern with the study design was the potential for bias in the search and recording of information from the patient chart. Ideally, the person collecting information from the patient chart would be 'blinded' with respect to the disease status of the patient to avoid biasing the collection of exposure information. Since 'blinding' was not practical in this study, the alternative was to design a data collection protocol that would effectively eliminate ambiguities in data collection and ensure an unbiased recording of information. The data collection protocol used in this study is given in Appendix B.

Also, data on certain factors was not available from the patient chart and could not be accounted for in the study. This included information on race, socioeconomic status, alcohol use, tobacco use, diet, and body mass index. For this study, the most important information that was unavailable was the patient's age at menopause. Although the Patient History form provided information on the type of menopause (natural or surgical) it did not specifically indicate the patient's age at menopause. Since a woman's age at menopause has been shown to affect her risk of breast cancer and may affect the decision to use replacement hormones, it is a potential confounding factor in assessing the risk of breast cancer from HRT use that was not controlled for in the study (Hayes 1993).

Finally, certain selection pressures existed in the study which ultimately limited the conclusions which could be drawn from the study results. This included the age of the study population and the possibility that women who were age 60 years and older and currently using HRT reached menopause later in life than women who were not currently using HRT. Also, women selected for the study were women with benign breast disease and who had clinical indications for biopsy. These women may have a different pattern of HRT use than the general population and also may be at differet overall risk of breast cancer than the general population of women.

I. Summary:

The primary purpose of this study was to determine if the risk of breast cancer in postmenopausal women having breast biopsies, as estimated by the odds ratio, is modified by interaction between mammographic radiation exposure and current use of replacement hormones. The study population consisted of women who were 60 years or older at the date of the reference pathology report and who had no personal history of breast cancer before their diagnosis at the study clinic. The study population was drawn from patients who had visited the clinic between 1989 and 1998 and consisted of 252 eligible cases and 342 eligible controls. All study subjects were diagnosed by histological examination of a biopsy sample and information on disease, exposures and potential confounding factors was obtained retrospectively from medical records in the patient chart. The study used a case-control design and estimated the relative risk of breast cancer as the odds ratio of HRT use and radiation exposure in cases to HRT use and radiation exposure in controls. The data was analyzed by logistic regression analysis using an application software program (SPSS 1994) and by stratified analysis using contingency tables.

Chapter 4

Results

A. Introduction:

The primary objective of this study was to determine if current HRT use modifies the risk of breast cancer associated with mammographic radiation exposure in older women having breast biopsies. In order to accomplish this, a model was developed which included major risk factors for breast cancer identified in the study population. The model attempted to control for potential confounding, and it also attempted to evaluate the potential interaction between the risk factors of interest.

The model was developed using logistic regression methods, however stratified analysis was also used to assess the importance of certain variables and to provide insight into the appropriate scale for each of the variables. The objective at the early stage of model development was to identify those risk factors which were either statistically significant or which had biological significance with respect to breast cancer. The goal was to develop the most parsimonious model which fit the data and in the process allowed testing of the study hypotheses. The following sections provide an account of how the data was analyzed and the results of the analysis.

B. Selection of Risk Factors:

Table 5 shows the percentage of selected characteristics among invasive breast cancer cases and controls in the study population. The characteristics chosen were based on previous studies of breast cancer but were limited by the information which was available in the study clinic.

There were 215 eligible cases of invasive breast cancer and 342 eligible controls used in the analysis. Cases and controls were similar with respect to some risk factors, although cases were more likely than controls to be over the age of 75 years. Cases were also more likely than controls to have a family history of breast cancer and to have had prior personal cancer other than breast cancer. Controls were more likely than cases to be younger than age 70, to have had a bilateral ovariectomy, and to have had current prescription medication use. Cases and controls were similar with respect to early age at menarche, nulliparity, prior hysterectomy, family history of nonbreast cancer and a history of benign breast disease.

With respect to the exposures of interest, a greater percentage of controls reported current HRT use than cases. Table 5 shows that 34.5 per cent of controls were currently using HRT on admission to the study clinic while only 22.3 per cent of cases were currently using HRT on admission. A larger percentage of controls than cases were currently using other prescription medication as well, with 69.9 per cent of controls and 61.4 per cent of cases reporting usage on admission.

In addition to a larger percentage of current HRT use, the mean duration of current HRT use was greater for controls than cases with invasive breast cancer. Table 6 shows that the control group had a mean duration of current HRT use of 51.8 months compared to 33.3 months for cases with invasive breast cancer and the difference was statistically significant ($p < 0.05$). However, cases with in situ breast cancer but no invasive component, had a greater mean duration of current HRT use greater than either cases with invasive breast cancer or the control group. The difference in the mean duration between the in situ group and the control group was not statistically significant however ($p > 0.10$).

A similar analysis was also conducted with respect to cumulative breast dose from mammographic radiation. Table 5 shows that a greater percentage of controls (84 per cent) had received past mammographic radiation exposure than cases (71 per cent), and as seen in table 7, controls had a greater mean cumulative breast dose than cases. However the difference in the mean cumulative breast dose was not statistically significant ($p > 0.25$) and was equivalent to just one additional mammogram.

To further explore these relationships, a univariate logistic regression analysis was carried out for HRT use, mammographic radiation dose and other risk factors of interest. In this analysis, each risk factor was assigned a three letter code shown in table 8. Variables were classified as either continuous or discrete and if discrete, the variable was assigned a set of integer values corresponding to the different categories or levels of the variable. AGE was treated as a continuous variable and limited to integer values of 60 or greater. DOS and DUR were treated as discrete variables rather than continuous variables. For DUR, this was done to reduce the effect of misclassification bias since the accuracy of reported HRT duration by patients could not be verified. For DOS, the cumulative breast dose was unknown for 61 per cent of the patients that were initially eligible for the study, leaving only 215 patients with information on both current HRT use and radiation exposure. Therefore it was not practical to treat DOS as a continuous variable. Instead the data was collapsed into discrete categories of DOS shown in table 8.

HRT use has been analyzed in some studies as a dichotomous variable (i.e. 'ever use' vs 'never use') and in other studies by taking into account the duration of use. To determine whether or not the risk of breast cancer varied with the duration of current HRT use in the study population, separate odds ratios were determined for durations of 1 to 120 months, 121 to 240 months, 240 to 360 months and for women with unknown duration of use. The odds ratios for these current HRT time periods is given in the univariate analysis shown in table 9. From this table, there does not appear to be any relationship between breast cancer risk and duration of current HRT use, although current

HRT use of any duration appears to result in a reduced risk of breast cancer. Therefore, due to the lack of an apparent trend in risk with duration of current HRT use, and because of the uncertainty of past HRT use other than current use, current HRT use was treated as a dichotomous variable and recoded as HRT ('yes' or 'no') in table 8.

Having selected a scale for each variable, the risk coefficient β, standard error of β, odds ratio, confidence interval, and associated p value for the wald statistic were determined for each variable shown in table 9. For AGE, the odds ratio was estimated for a ten year increase. At this stage in the analysis, variables were considered as potentially important if the wald statistic p value was less than 0.25. Hosmer and Lemeshow suggest using this value for initial screening purposes because use of the more traditional value of 0.05 often fails to identify variables which are important in the analysis (Hosmer 1989).

Based on this criteria, AGE, OVR, FBC, PCA, HRT and DOS were retained in the model, while MEN, PAR, HYS were excluded from further analysis. BBD and FCA were also retained in the model because of their potential to cause confounding of the risk estimate for current HRT use and mammographic breast dose. The confidence interval for all of the excluded variables included the null value supporting the decision to exclude these variables from the analysis. For variables which were retained in the model, a moderate level of statistical significance was found for one or more levels of the variable.

From the univariate analysis it can be seen that women with a bilateral ovariectomy and women with current HRT use had a significantly reduced risk of being diagnosed with breast cancer. Women with a family history of breast cancer or other cancer and women with a personal history of cancer had a nonsignificant elevated risk of being diagnosed with breast cancer. Older women had an elevated risk of being diagnosed with breast cancer that was statistically significant and women with past radiation dose to the breast had a reduced risk of being diagnosed with breast cancer which was statistically significant for the lowest dose stratum.

As seen in table 9, the risk of a diagnosis of breast cancer increased with increasing cumulative breast dose except for the upper dose stratum in which the risk decreased. However, the relative risk confidence intervals for the different levels of cumulative dose overlapped considerably, which suggests that the trend in risk with dose may have been due to chance.

C. Fitting the Multivariate Logistic Regression Model:

Following the univariate analysis, a multivariate logistic regression analysis was carried out, but only for the women with a known cumulative breast dose. This reduced the number of women available for the analysis and consequently reduced the power to detect significant differences in risk. The results of the multivariate analysis for women of known breast dose are shown in table 10.

From this table it can be seen that after adjusting for other risk factors, AGE and BBD were associated with a moderate increased risk of breast cancer diagnosis (odds ratio = 1.14 and 1.37 respectively), while PCA was associated with a greatly increased risk of breast cancer diagnosis (odds ratio = 6.12). However, only PCA showed a significantly elevated risk of breast cancer diagnosis (confidence interval; 1.10 - 34.20).

After adjustment for other factors, FBC and FCA failed to show even a moderate association with breast cancer diagnosis. Also, the risk estimates and confidence intervals for these two factors were nearly identical (odds ratio = 1.05 for FBC and odds ratio = 1.06 for FCA).

OVR, HRT and DOS were associated with a reduced risk of a diagnosis of breast cancer in the study population. For OVR, the association was stronger for women with a bilateral ovariectomy (odds ratio = 0.72) than for women with a unilateral ovariectomy (odds ratio = 0.91). Neither was statistically significant, however. HRT was also associated with a reduced risk of breast cancer diagnosis in the study population but this association was not statistically significant after adjustment for the other risk factors (odds ratio = 0.54; 95% C.I. = 0.27 - 1.10).

DOS also showed a non significant association with breast cancer diagnosis. Women in the study population who had received mammographic radiation exposure had a reduced risk of being diagnosed with breast cancer compared to women who had no previous mammographic radiation exposure. This association was found for all radiation dose levels except for women in the 1201 to 1600 mrad dose category. However, there were only four women in this upper dose category and the odds ratio confidence interval was large (95 C.I. = 0.13 - 10.25). Although there appeared to be an increased risk of breast cancer with increasing dose, the confidence intervals for the dose categories showed considerable overlap due to the relatively small number of patients in each dose category. Therefore, no conclusion could be made with respect to a dose response relationship among the study population.

D. Test for Interaction:

The variables which were included in the multivariate model were also tested for possible interaction with each other and the results are shown in table 11. The test which was used to determine the significance of each interaction term in the logistic regression model was the log-likelihood ratio test. This test was performed by determining the difference between the log-likelihood value of the multivariate model and the log-likelihood value of the multivariate model with an interaction term included. The difference in the log-likelihood values is equal to the G statistic which follows a chi-square distribution and has degrees of freedom equal to the difference in the number of variables between the two models.

From table 11 it can be seen that the only interaction terms which were statistically significant were OVR x HRT ($0.02 > p > 0.01$) and FCA x HRT ($0.05 > p > 0.02$). However these variables did not interact with the other variables in the model.

Of particular interest, was the interaction term HRT x DOS. As can be seen in table 11, the value of the log-likelihood ratio test statistic G for this interaction term was equal to 5.974 with 7 degrees of freedom. The corresponding p value was greater than 0.20 indicating that HRT x DOS was not a statistically significant interaction term. Therefore, there was no evidence of interaction between hormone replacement therapy and mammographic radiation dose affecting the risk of a diagnosis of breast cancer in the study population.

To confirm this finding, a stratified analysis was performed by cross tabulation of the data rather than using logistic regression. Table 12 shows that the odds ratio for a diagnosis of breast cancer associated with current HRT use did not change significantly with radiation dose ($p > 0.50$). Although women with a cumulative breast dose greater than 800 mrad had an increased relative risk of breast cancer from HRT use compared to women with 1 to 800 mrad, there was considerable overlap of the confidence intervals of these strata. Furthermore, the estimated risk of breast cancer associated with HRT use for women in the upper dose stratum (odds ratio = 0.85) was essential equal to the estimated risk of breast cancer associated with HRT use for women in the zero dose stratum (odd ratio = 0.83).

A similar analysis was performed to determine if the risk of a diagnosis of breast cancer associated with mammographic radiation dose was modified by HRT use. Table 13 shows the estimated risk of breast cancer associated with radiation dose stratified by current HRT status in the study population. For women who reported no current HRT use, the risk of a positive finding of breast cancer associated with radiation dose was 0.77 (95% C.I.; 0.38 to 1.56) and for women who reported current HRT use, the risk of a positive finding of breast cancer associated with radiation dose was 0.45 (95% C.I.; 0.12 to 1.63). However, the confidence intervals of these HRT strata had considerable overlap and a chi-square test of homogeneity indicated no significant difference in the stratum-specific odds ratios ($p > 0.20$).

D. Model for Invasive Breast Cancer in the Study Population:

Based on the results of the log-likelihood ratio test for the various terms considered in the analysis, a model for invasive breast cancer was fit which included the risk factors AGE, OVR, FBC, FCA, PCA, BBD, HRT and DOS. Also included, were the interaction terms OVR x HRT and FCA x HRT which were found to be statistically significant. Table 14 provides the odds ratio and confidence intervals for each of the risk factors in the multivariate model containing the interaction terms.

The addition of these two interaction terms to the multivariate model resulted in a change in risk estimate for some of the variables in the model. A comparison of table 10 and table 14 shows that the addition of the interaction terms OVR x HRT and FCA x HRT changed the magnitude but not the direction of the estimated risk for most of the variables in the model. Addition of the interaction terms to the multivariate model also increased the size of the confidence intervals for all of the variables in the model.

E. Hormone Type and of Stage of Disease Effects:

An analysis of the risk of breast cancer stratified by hormone type and stage of disease was also conducted. Table 15 provides adjusted risk estimates associated with current HRT use stratified by the type of HRT used and table 16 provides adjusted risk estimates associated with current HRT use when stratified by the stage of breast cancer.

Women in the study population who reported current use of estrogen alone were less likely to be diagnosed with breast cancer than women who reported no current HRT use (odds ratio = 0.46; 95% C.I.= 0.01 - 2.37). However, women who reported current use of estrogen combined with progestin were more likely to be diagnosed with breast cancer than women who reported no current HRT use (odds ratio = 1.69; 95% C.I. = 0.12 - 23.54). However, there were only 8 women who reported estrogen-progestin use and its confidence interval overlapped considerable with the confidence interval of the estrogen only stratum.

When the analysis was stratified by type and stage of breast cancer, women reporting current HRT use were more likely to be diagnosed with in situ breast cancer than women who reported no current HRT use (odds ratio = 5.09; 95% C.I. = 0.11 - 241.06). Also, women who reported current HRT use were more likely to be diagnosed with breast cancer that had spread to the lymph nodes (stage II breast cancer) than women who reported no current HRT use (odds ratio = 1.40; 95% C.I. = 0.03 - 66.21). However, women who reported current HRT use were less likely to be diagnosed with breast cancer that had not spread to the lymph nodes (stage I breast cancer) than women who reported no HRT use (odds ratio = 0.22; 95% C.I. = 0.04 - 1.30). None of these results were statistically significant, however.

In addition to stratifying by the stage of disease, risk estimates for current HRT use were also stratified by tumour size as shown in table 17. There was a general increase in the odds ratio with increased tumour size, however the stratum-specific risk estimate confidence intervals overlapped considerably and none of the stratum-specific risk estimates were statistically significant.

The distribution of invasive tumour size as a continuous variable is shown in table 18. To assess the effect of current HRT use on mammographic sensitivity, tumour size in cases reporting current HRT use was compared to tumour size in cases reporting no current HRT use. For all stages of breast cancer combined, the tumour size distribution for women reporting current HRT use was similar to the distribution for women reporting no current HRT use. Stage I breast cancer cases (i.e. negative nodes) reporting current HRT use tended to be diagnosed with larger invasive tumours than stage I cases reporting no current HRT use. For stage II breast cancer cases (i.e positive nodes), the opposite was found with women reporting current HRT use diagnosed with smaller tumours than women reporting no current HRT use. None of the mean tumour size differences between current HRT users and non users were statistically significant, however ($p > 0.10$).

F. Summary of Study Results:

The objective of this study was to determine if current HRT use modifies the risk of breast cancer associated with mammographic radiation exposure in older women having breast biopsies. Alteration of risk is possible by either effect modification or confounding, therefore the analysis consisted of developing a logistic regression model that contained terms found to be either statistically significant or biologically important to the risk of breast cancer in the study population.

Based on the relative frequency of various characteristics in the study population, it was shown that cases were somewhat older than controls and were more likely to have had a family history of breast cancer or prior personal cancer. Controls were more likely to have had a bilateral ovariectomy, to have used prescription medications including replacement hormones, and to have received past mammographic radiation exposure.

A univariate logistic regression analysis of each risk factor showed that age, ovariectomy status, family breast cancer history, prior personal cancer, current HRT use and mammographic dose were potentially important factors in determining risk of a positive diagnosis of breast cancer in the study population. Age at menarche, parity, hysterectomy status and history of benign breast disease were not found to be statistically important factors in the univariate analysis, however benign breast disease and family cancer history were potentially important confounding factors and were included in for further analysis in the study.

A multivariate logistic regression fit to the variables AGE, OVR, FBC, FCA, PCA, BBD, HRT and DOS showed that age at biopsy, a history of personal cancer, and a history of benign breast disease were associated with an increased risk of being diagnosed with breast cancer in the study population. For past personal cancer, the risk was significantly elevated (odds ratio = 6.12; 95% C.I. = 1.10 - 34.20).

Conversely, current HRT use, a bilateral ovariectomy and past mammographic exposure were associated with a reduced risk of diagnosis of breast cancer in the study population. No association was found between family cancer history and the risk of a positive diagnosis of breast cancer in the study population.

In addition to identifying individual risk factors for breast cancer in the study population, the possibility of interactions was investigated. No significant interactions were found for AGE, FBC, PCA, BBD or DOS but an interaction was found between OVR and HRT and between FCA and HRT that was statistically significant ($p < 0.05$). Of particular interest to the study was the possible interaction between HRT and DOS. However, a test for interaction using the log-likelihood ratio test showed the interaction term HRT x DOS to be non significant ($p > 0.20$). Similarly, a test for effect modification by stratified analysis showed that current HRT use did not modify the risk of a positive diagnosis of breast cancer associated with past mammographic radiation exposure in the study population ($p > 0.20$). Therefore the null hypothesis of no interaction between HRT and DOS could not be rejected.

The study also investigated potential differences in risk associated with estrogen alone versus estrogen-progestin. Although current use of estrogen-progestin was associated with a greater risk of a diagnosis of breast cancer (odds ratio = 1.69) than current use of estrogen alone (odds ratio = 0.46), the relatively small size of the study population used in this analysis (n = 215) resulted in risk estimates that were not statistically significant for either hormone preparation.

Finally, separate risk estimates were determined for in situ, stage I (negative nodes) and stage II breast cancer (positive nodes). Women reporting current use of HRT were at greater risk of being diagnosed with in situ breast cancer than women reporting no current HRT use (odds ratio = 5.09). Also, women reporting current HRT use were at greater risk of being diagnosed with positive lymph nodes (stage II breast cancer) than women reporting no current HRT use (odds ratio = 1.40). However, neither result was statistically significant, in part due to the small size of the study population included in the analysis.

Chapter 5

Discussion

A. Overview of the Study:

The objective of this study was to determine if current HRT use modifies the risk of breast cancer associated with mammographic radiation exposure in postmenopausal women having breast biopsies. To test this hypothesis, a case-control study was conducted of women who utilized the services of a diagnostic breast imaging clinic in the city of Edmonton between 1989 and 1998 and whose diagnosis was determined by histological examination of a biopsy sample. Women were eligible for the study if they were age 60 or older and if they had no prior history of breast cancer.

Of the 24,420 patient charts in the study clinic, only 252 cases and 342 controls met the eligibility criteria of the study. Of these women, only 103 cases and 112 controls had a cumulative breast dose that could be determined from the data in the patient charts. According to the sample size calculation, 159 cases and 159 controls were required to detect a relative risk of breast cancer from HRT use equal to 1.50 or greater with 95 per cent confidence and 80 percent power of detection. A relative risk of this magnitude was within the range estimates of previous studies (Steinberg 1994) and the original number of cases (n= 252) and controls (n = 342) was sufficient to detect this level of risk. However, after the data was collected, there were not enough cases (n = 103) or controls (n = 112) with known cumulative breast dose, to detect a relative risk of 1.50 from HRT use. Therefore, the power to detect differences in risk with small changes in the HRT or radiation exposure was quite limited in this study.

All of the information on patient characteristics, exposures of interest and diagnoses was obtained retrospectively from patients charts in the study clinic. No follow-up interviews were conducted and no medical records were available from outside the study clinic. Therefore, the validity of some of the information in the patient chart was difficult to assess, and this influenced the manner in which the data was handled in the analysis. For example, when durations of exposure were recorded in the patient chart, it was sometimes necessary to collapse the data into categories of exposure in order to reduce the error and preserve the validity of the findings. However, the data was always collected as it was presented in the patient chart and was not collapsed until the analysis stage of the study.

A patient data summary form was used to collect the data and explicit instructions were followed to reduce data collection bias. In order to gain experience in using the data collection instructions, several dozen patient charts were randomly selected for testing the data collection protocol. In this manner, ambiguities in the data collection instructions were identified and eliminated prior to the collection of data used in the analysis. Additionally, the data collector interviewed staff at the study clinic including the radiologist, in order to gain familiarity with the forms found in the patient chart and to better understand how the data was presented.

B. Overview of the Results:

An examination of table 5 shows that the cases and controls in the study were similar with respect to a number of the breast cancer risk factors that were measured. Exceptions to this were the higher percentage of cases than controls over the age of 75 years, and the higher percentage of controls than cases with a bilateral ovariectomy. These observations are not surprising since breast cancer in North American women has been shown to increase with increasing age, and events which reduce serum levels of estrogen such as a bilateral ovariectomy, have been shown to reduce the risk of breast cancer (Hayes 1993, Iqbal 1989, Kelsey 1988).

Other factors such as age at menarche and nulliparity, which have been shown to be associated with an increased risk of breast cancer in other studies, showed no apparent association with breast cancer in the study population.

Early age at menarche (i.e. before age 12) is a suspected risk factor for breast cancer since it increases the number of reproductive years in a woman's life and the length of time that breast tissue is exposed to the possible tumour promoting effects of endogenous estrogen (Hayes 1993). The association of breast cancer risk with nulliparity follows a similar line of thought in that nulliparous women have a greater number menstrual cycles in their reproductive lives and longer exposure time to endogenous estrogen than women who have had one or more pregnancies. The lack of association of these factors with breast cancer in the study population could be due to differences between the controls in the study and the general population. Since age at menarche and nulliparity are only moderately associated with breast cancer (relative risk = 1 to 2), differences between the study population and the general population could obscure the underlying relationship between these risk factors and breast cancer.

Benign breast disease has also been associated with an increased risk of breast cancer, especially in women with atypical hyperplasia (Dupont 1989). In this study, information on the histological characteristics of past benign breast disease were not available from the patient history records. The lack of construct validity and the potential for misclassification bias could explain the failure to observe a large difference in the relative frequency of benign breast disease between cases (10.7 %) and controls (12.9 %) in the study population. Also, the patients selected for the study, were patients who had sufficient radiological indications for a breast biopsy and many of these patients came to the study clinic on account of symptoms associated with benign breast disease. Therefore it is not surprising that the controls in this study had a slightly greater relative frequency of benign breast disease than the cases in the study.

Prior hysterectomy was not found to be associated with breast cancer in the study population even though some previous studies have shown women with hysterectomies to be at reduced risk of breast cancer (Trichopoulos 1972). However, it has been suggested that the reduced risk of breast cancer may actually be due to ovariectomies performed at the same time as the hysterectomy (Baum 1994, Burch 1974). In this study a reduced risk of a diagnosis of breast cancer was found for women who had received a bilateral ovariectomy (odds ratio = 0.78) which is consistent with the results of previous studies.

An increased risk of breast cancer in the study population was found for women with a family history of breast cancer or other cancer (unadjusted odds ratio = 1.23) as shown in table 9. Women with a family history of breast cancer in the study population had an increased risk of breast cancer (unadjusted odds ratio = 1.38) that was not statistically significant (95% C.I. = 0.92 - 2.06) but sufficiently skewed to suggest the presence of an association. Women with a family history of nonbreast cancer were also found to have an increased risk of breast cancer although the increase was not statistically significant (unadjusted odds ratio = 1.23; 95% C.I. = 0.81 - 1.86). The principal types of family cancer associated with breast cancer are cancers of the breast, ovary and prostate gland and although these were identified during data collection, there was an insufficient number for subgroup analysis.

The relative frequency of prior personal cancer was greater among cases (8.4 %) than controls (5.0 %) as seen in table 5. Although the estimated risk was not statistically significant in the univariate analysis of table 9, it was sufficiently skewed to suggest an association with breast cancer (unadjusted odds ratio = 1.87; 95% C.I. = 0.94 - 3.73). As with family cancer history, there was not enough patients with prior cancer to allow subgroup analysis, even though certain types of cancer (e.g. ovarian) correlate more strongly with breast cancer than others types.

As seen in table 5, controls had a higher relative frequency of HRT use (34.5 %) and mammographic exposure (83.9 %) than cases (22.3 % for HRT and 71.0 % for mammography). HRT use was measured as 'current use' versus 'no current use' in this table and mammographic utilization was measured as 'any prior mammogram' versus 'no prior mammograms'. Table 6 and 7 show that the mean duration of current HRT use and the mean cumulative breast dose were also greater among controls than cases. Table 9 shows that current HRT users had a significantly reduced risk of breast cancer diagnosis (unadjusted odds ratio = 0.60; 95% C.I. = 0.40 - 0.89) compared to women who reported no current HRT use and that mammographic exposure was associated with a reduced risk of breast cancer diagnosis at all dose levels in the study population. For radiation dose, the unadjusted risk estimates were nonsignificant for all dose levels except for the lowest dose stratum (1 - 400 mrad) probably due to the small number of patients in the upper dose strata.

Without adjusting for potential confounding, the finding of a reduced risk of breast cancer from HRT use and mammographic exposure could not be interpreted as a protective effect or even that an association was present. The presence of uncontrolled confounding or bias within the study could account for the reduced risk observed for either of these exposures. In the case of mammographic exposure, all but the lowest dose level had confidence intervals which included the null value and could have been due to chance. However, for the lowest dose group (1 - 400 mrad), a significant reduction in risk was found (odds ratio = 0.51; 95% C.I. = 0.26 - 0.99) indicating that the reduced risk could not be explained by statistical variation alone. Therefore, the reduced risk from low dose radiation and HRT use could not be given as evidence of hormesis (i.e. a protective effect) without adequate consideration of uncontrolled confounding or bias in the study.

The unadjusted risk estimates for current HRT use and radiation dose shown in table 9 were potentially confounded by a number of factors in the study population. Potential confounding factors included age at biopsy, age of menopause, type of menopause, family breast or other cancers, prior personal cancer and benign breast disease history. Also, current HRT use and mammographic exposures were potential confounding factors of each other. Information was available from the patient records on all of these potential confounding factors except age at menopause.

Age at menopause is a suspected risk factor for breast cancer in that women who have a later age at menopause are exposed to a greater number of menstrual cycles and a greater total duration of endogenous estrogen. Age at menopause may also be associated with the age at which HRT use begins. For women who begin menopause at an earlier age, they may be a lower risk of breast cancer than women with a later age at menopause. This could negatively confound risk estimate of breast cancer associated with duration of HRT use. Age at menopause was not reported in the patients records of the study population, therefore the confounding effect of this factor on the estimate of HRT risk could not be controlled. This ultimately reduced the ability of the study to draw conclusions from the association observed between current HRT use and the risk of breast cancer in the study population. Women that reported shorter durations of current HRT use, may have reached menopause at a later age than women of the same age who reported longer durations of current HRT use. If this were true, then the protective effect of early age at menopause may have offset an increased risk with longer duration of HRT use making it appear that that there was no change in risk with change in duration of HRT use.

Age at menopause may also have confounded the association between breast cancer risk and mammographic radiation dose. Women who reach menopause earlier in life, may begin receiving regular mammograms at an earlier age as well, based on changes in breast density favoring the use of mammography over other detection techniques such as ultrasound. However, the protective effect of an earlier age at menopause may offset any increased risk of breast cancer associated with increased mammographic utilization.

Therefore, age at menopause had the potential to confound breast cancer risk estimates for both HRT and radiation exposure and without knowledge of the age at menopause in the study population, the study results had to be interpreted with considerable caution.

Another problem with the study which tended to limit the interpretation of its results was the age of the women selected for the study. Women were selected who were age 60 years and older because information on the age of menopause was unknown, and the intention was to include only postmenopausal women in the study. The problem with this approach was that it also tended to increase the possibility of misclassification bias in the study. Many women tend to use HRT immediately after menopause and since the study population was on average, nine years postmenopausal, it increased the period of time over which HRT may have been used prior to entry into the clinic. If the HRT usage was stopped prior to entry to the clinic, these women would have reported no current HRT use and since the only information available was information on current use of HRT, past use of HRT would have gone unreported. If past use of HRT is a risk factor for breast cancer, this would have resulted in misclassifying women with respect to HRT exposure and reduced the validity of the study findings.

With these limitations in mind, an attempt was made to control for those confounding factors such as age at biopsy, and ovary status for which information was available. For this purpose, a logistic regression analysis of the data was carried out to determine if mammographic radiation and current HRT use are risk predictors of breast cancer in the study population and if interaction between these factors modifies the risk estimate. As shown in table 10, a multivariate logistic regression was performed on variables which showed at least a moderate level of association with breast cancer in the univariate analysis or were potential confounding factors for the estimates of HRT and mammographic radiation risk.

The factors chosen for the multivariate model included AGE, OVR, FBC, FCA, PCA and BBD. It was decided to include only women with a known cumulative breast dose in the multivariate model since the objective of the study was to examine the possibility of interaction between current HRT use and mammographic dose, and for this, information on dose was required. Unfortunately, the cumulative breast dose could not be determined with certainty for 369 of the original 594 eligible study subjects, leaving only 225 patients available for the multivariate analysis. This greatly reduced the ability to detect significant effects in the multivariate model and further limited the ability to draw conclusions from the study results. As can be seen from table 10, the only risk estimate that was obtained with statistical significance was PCA (odds ratio = 6.12), but even for that factor the confidence interval was quite large (95% C.I. = 1.10 - 34.2).

For OVR, women that received a bilateral ovariectomy were less likely to be diagnosed with breast cancer than women who had a natural menopause (odds ratio = 0.72; 95% C.I. = 0.28 - 1.82). This association was not as strong for women with a unilateral ovariectomy (odds ratio = 0.91; 95% C.I. = 0.25 - 3.32) as might be expected based on studies which have shown that surgical menopause is protective primarily for women with bilateral ovariectomies.

After adjustment for other factors, FBC and FCA showed only a slight increase in risk of breast cancer diagnosis in the study population even though a history of family breast cancer or other cancers has exhibited moderate to strong association with breast cancer in other studies. The lack of a positive association after adjustment could have been due to the reduced number of patients included in the multivariate analysis compared to the univariate analysis, which with more patients, showed a stronger association between these risk factors and breast cancer. Also, a certain degree of misclassification may have occurred, especially if some of the patients were uncertain of their family cancer history and had provided incorrect information on the patient history form. Furthermore, only certain types of family breast cancer or other cancers have shown strong associations with breast cancer and given the limited number of patients in the study, it was not possible to stratify the analysis along these lines.

After adjustment for other factors, a large association was found between personal cancer (non breast) history (odds ratio = 6.12) and breast cancer. This association was much larger than what was found in the univariate analysis (odd ratio = 1.87) and was probably due to statistical fluctuation within the small sample size of the multivariate model.

For BBD, the direction of association changed from the univariate analysis (odds ratio = 0.84) to the multivariate analysis (odds ratio = 1.37). However, the risk estimates were not statistically significant and the variation was probably due to statistical fluctuation within the small sample size since only 10.7 per cent of the cases and 12.95 per cent of the controls reported past symptoms associated with benign breast disease.

For current HRT use, the magnitude and direction of the risk estimate did not changed substantially from the univariate model (odds ratio = 0.60) to the multivariate model (odds ratio = 0.54). However, the risk estimate in the multivariate model was not statistically significant (95% C.I. = 0.27 - 1.10) as it was in the univariate analysis (95% C.I. = 0.40 - 0.89) but this was probably due to the smaller number of patients in the multivariate model (n = 225) compared to the univariate model (n = 594).

This result is not inconsistent with other case control studies which have used biopsied patients. Horwitz and Stewart studied the effect of different clinical features on the relative risk of estrogen use among 257 cases and 664 controls and the results of this study are shown in table 2 (Horwitz 1984). The apparent reduction in risk with current HRT use in the study population could be due to selection bias in the study. The women used in this study were age 60 years and older and were seen at the study clinic because of breast symptoms. If an association exists between breast symptoms and current HRT use, it is possible that the apparent protective effect of current HRT use, was due to the use of controls who were different from the general population of women with respect to HRT use or its side effects. Also, as indicated earlier, age at menopause was not known for the study subjects and could have been a source of uncontrolled confounding of the risk estimate of current HRT use.

For DOS, the risk estimates in the multivariate model tended toward the null value compared to the same risk estimates in the univariate analysis. Since the number of patients in each dose category was the same for the univariate and multivariate model, the change in risk estimate toward the null value in the multivariate model suggests that the "protective effect" observed in the univariate model was due to confounding that was adjusted for in the multivariate model. It is possible that women using HRT are more likely to receive mammograms and the apparent decrease in risk of breast cancer among women receiving mammograms may have been due to the association of mammograms and HRT use. As explained earlier, the apparent decrease in risk of breast cancer from current HRT use may have been due to controlled confounding or selection bias in the study. Therefore, it seems reasonable to conclude that at least part of the reduced risk found among women with past mammographic exposure was due to residual confounding in the study. The monotonic increase in risk with increase in dose seen in table 10 is probably due to chance since the confidence intervals overlap considerably. Furthermore, there is no evidence from past studies that a radiation dose increase of 1200 mrad would result in a measurable change in the risk of breast cancer. The lowest dose at which an elevated risk of breast cancer was observed in any of the studies of atomic bomb or medical exposures was 20,000 mrad (NRC 1990).This is well above the maximum cumulative breast dose found in the present study population.

In the study performed by Mattsson of women treated for benign breast disease with medical x-rays, a significant dose-response gradient of 8.3 E - 06 per mrad was observed for women receiving breast doses ranging from 20,000 to 200,000 mrad (Mattsson 1993). Assuming that the risk coefficient found in Mattsson's study can be applied to the present study, the expected relative risk increase for a dose increase of 1200 mrad would be equal to exp (8.3 E - 06)(1200) - exp(8.3 E - 06)(0) = 1.012 - 1.00 = 0.012.

The actual relative risk increase found for an increase of 1200 mrad was determined by subtracting the estimated odds ratio of dose level 4 from the odds ratio of dose level 1, which is equal to 1.13 minus 0.64 = 0.49. Comparison of the actual and expected increases in relative risk, indicates that the observed increase in relative risk (0.49) was much greater than expected (0.012). To account for a relative risk increase of 0.49 would require a dose increase of $(8.3 \text{ E} - 06)^{-1}$ ln (1.49) = 48, 045 mrad which is well above the maximum cumulative dose found in this study. Therefore, it is unlikely that the observed increase in relative risk was due to an increase in dose. It is more likely that the observed increase in relative risk with increase in cumulative breast dose was due to chance.

To test for possible interaction between each of the terms in the multivariate model, log-likelihood ratio tests were performed as shown in table 11. No interactions were found for age at biopsy, family breast cancer history, personal cancer history, benign breast disease history or cumulative breast dose in the study population. A significant interaction was found between type of menopause and current HRT use ($0.02 < p < 0.01$) represented as OVR x HRT in table 11. This indicates that the effect of one these risk predictors is modified by the level of the other risk predictor. For instance, the risk estimate associated with HRT use may have been modified by the type of menopause of the patients in the study population, or conversely, the risk estimate of menopause type may have been modified by current HRT status of the patients. The other significant interaction that was found was between family cancer history and current HRT use ($0.05 > p > 0.02$) as represented by FCA x HRT in table 11. This interaction could be interpreted as a modification of the risk estimate of HRT for study subjects with different family histories of cancer.

Of particular interest to the study was determining if interaction existed between current HRT use and cumulative breast dose. However, as seen from table 11 the interaction term HRT x DOS was not found to be statistically significant ($0.80 > p$ 0.20).Thus, the null hypothesis of no interaction between HRT use and mammographic dose could not be rejected based on this test for effect modification.

As an additional test for effect modification, the odds ratio associated with HRT use was determined for two levels of radiation dose, and a chi-square test of homogeneity performed to see if the odds ratios were different. Table 12 shows the odds ratios of breast cancer from HRT use estimated for women with a cumulative breast dose of 1 to 800 mrad and greater than 800 mrad. If radiation dose potentiates the carcinogenic effect of HRT, an increase in HRT risk should be observed at higher radiation dose levels.

The odds ratio of breast cancer from HRT use did increase in the upper dose stratum (odds ratio = 0.85) relative to the lower dose stratum (odds ratio = 0.43) which is what would be expected if interaction between HRT and radiation had occurred. However, the difference in the odds ratios could easily have been due to chance since the confidence intervals overlapped considerably and a chi-square test of homogeneity showed the difference to be nonsignificant ($p > 0.50$).

A similar analysis was conducted to test the potential for HRT use to modify the risk of breast cancer from mammographic radiation. Table 13 shows the odds ratios of breast cancer from 'any' mammographic radiation for women using HRT and not using HRT. Again, if effect modification were occurring, a difference in the stratum-specific odds ratios should be observed. In this instance, HRT use appeared to reduce the risk of breast cancer from radiation dose. The odds ratio of breast cancer associated with mammographic radiation was lower in the HRT user group (odds ratio = 0.45) than in the non user group (odds ratio = 0.77). Not only was the difference not significant according to a chi-square test of homogeneity ($p > 0.20$), but the change in the odds ratio was the opposite of what would be expected if HRT use potentiated the carcinogenic effect of radiation dose.

Therefore, there was a lack of evidence of an interaction between HRT and ionizing radiation capable of modifying the risk of a positive diagnosis of breast cancer in the study population. However this does not rule out the possibility of an interaction at higher radiation dose levels than were found in this study, or if a larger sample size was available. The observed increase in HRT risk at the higher dose level shown in table 12 suggests that a larger sample size might have revealed a significant interaction between HRT use and radiation dose in the study population.

The final model for breast cancer in the study population included AGE, OVR, FBC, FCA, PCA, BBD, HRT, DOS and the interaction terms OVR x HRT and FCA x

HRT. The odds ratios and confidence intervals for main effects are given in table 14. Adding the interaction terms to the multivariate model, resulted in an increase in the odds ratio and associated confidence intervals for all of the risk factors in the model with the exception of HRT for which no substantial change in the odds ratio was observed. In this final model, age at biopsy, family breast cancer or other cancer, prior personal cancer and benign breast disease were found to be positive predictors for a diagnosis of breast cancer in the study population. This result is consistent with other studies which have found each of these factors to be risk predictors of breast cancer (Hayes 1993).

A 22 per cent reduced risk of breast cancer was found for women with a bilateral ovariectomy after adjustment for other factors and the addition of the interactions terms in the model. Since a bilateral ovariectomy results in the immediate cessation of estrogen production, it is consistent with other evidence that events such as early menopause, which reduce the total exposure of breast tissue to endogenous estrogen, reduce the risk of breast cancer (Kampert 1988). A bilateral ovariectomy is almost always associated with HRT use. Therefore in estimating the risk of breast cancer in women with bilateral ovariectomies and in women with HRT use, the potential confounding effects of these two factors on each other was accounted for in the study.

After adjustment for other factors, current HRT use was found to be associated with a 36 percent reduced risk of breast cancer in the study population (odds ratio = 0.66; 95% C.I. = 0.43 - 1.00). This finding does not exclude the possibility that the reduced risk was due to selection bias or uncontrolled confounding in the study population as previously discussed. If the cases and controls in the study population were different with respect to an unknown breast cancer risk factor that was also associated with HRT use this could explain the apparent 'protective' effect from HRT use.

To further investigate the relationship of breast cancer diagnosis and current HRT use in the study population, the risk of breast cancer was stratified by hormone type. Table 15 gives the odds ratios and associated confidence intervals for current use of estrogen alone and current use of estrogen combined with progestin. Women in the study population who reported current use estrogen alone were 54 per cent less likely to be diagnosed with breast cancer than women who reported no current HRT use. Women who reported current use of estrogen-progestin on the other hand, had an estimated 69 per cent increase chance of being diagnosed with breast cancer. Neither of these results were statistically significant however, and the confidence intervals of the risk estimates had considerable overlap. There were only 8 women who reported current use of estrogen progestin among the 215 patients included in the analysis, therefore the elevated odds ratio could easily have been due to chance. It is nevertheless interesting that such a difference was found between current use of estrogen alone, and current use of estrogen-progestin. Several other studies have also found an increased risk of breast cancer among patients reporting current use of estrogen-progestin. Colditz found a relative risk of 1.41 for current estrogen-progestin use (Colditz 1995) and Ewertz found a relative risk of 1.36 for 'ever use' of estrogen-progestin (Ewertz 1988). However, not all studies have found an increased risk of breast cancer with estrogen-progestin use (Risch 1994, Stanford 1995) and the results of this study are far from unequivocal regarding the risk of estrogen-progestin.

In addition to possible variations in risk with hormone type, variations in the risk of different types and stage of disease were also examined. Table 16 shows the odds ratios and associated confidence intervals for in situ breast cancer and invasive breast cancer stratified by stage of disease. Here, stage I invasive breast cancer refers to a finding of negative lymph nodes at diagnosis and stage II invasive breast cancer refers to a finding of positive lymph nodes at diagnosis.

After adjustment for other factors, it was found that women reporting current HRT use were more likely to be diagnosed with in situ breast cancer than women reporting no current HRT use (odds ratio = 5.09; 95% C.I. = 0.11 - 241.06). This result was not significant however, and the confidence interval was exceptionally large reflecting the small number of cases diagnosed with in situ breast cancer in sample analyzed.

For invasive breast cancer, there was an increased risk for women diagnosed with positive lymph nodes who reported current HRT use compared to women who reported no current HRT use (odds ratio = 1.40; 95% C.I. = 0.03 - 66.21). This result was also non significant, however it was substantially elevated above the risk for a diagnosis of stage I breast cancer (odds ratio = 0.22; 95% C.I. = 0.04 - 1.30). One possible explanation for the difference in risk with stage of disease is that current HRT use reduces the sensitivity of mammograms to detect small invasive tumours and therefore women using HRT are more likely to be diagnosed at a more advanced stage of disease. There have been studies which suggested that current HRT use may increase the density or change the parenchymal pattern of breast tissue in postmenopausal women (Berkowitz 1990, Laya 1995). If this is true, then the change in breast density may reduce the sensitivity of mammograms for detecting breast lesions and it might explain the apparent difference in risk found for detection of stage I and stage II breast cancer found in this study.

To explore this further, the odds ratio was determined for several strata of invasive tumour size as shown in table 17. Although none of the stratum-specific odds ratios shown here were statistically significant, the point estimates of risk increased monotonically for the first three strata of tumour size, suggesting a possible association between current HRT use and increased tumour size detected. This interpretation must be taken with caution however since the sample size was small and the results could easily have been due to chance. Table 18, shows the distribution of invasive tumour sizes detected among the biopsied women in the study population. As seen from this table, no apparent difference in mean tumour size was found for women reporting current HRT use and the women reporting no current HRT use ($p > 0.10$). Therefore, the difference in risk found for stage I and stage II breast cancer in this study was probably due to chance as indicated by the large confidence intervals around the point estimates of risk.

There were several aspects of this study which reduced the ability to interpret the data and limited the degree to which conclusions could be drawn. As previously noted, there were several indications that the type of controls chosen for the study resulted in a biased reduction in the estimated risk of breast cancer from HRT use and radiation exposure. Evidence of this comes from the observation that controls had a greater relative frequency of HRT use, mammography and prescription medication use than cases. This finding suggests that the controls in the study represent a subgroup of women from the general population with a greater tendency to use medical services.

This type of selection bias has been described elsewhere (Steinberg 1994) and appears to occur more often when hospital controls are used in a case-control study. Hospital controls may also have medical conditions associated with the exposure of interest (Steinberg 1994). For example, it is possible that certain benign breast conditions which require radiological diagnosis may be associated with HRT use (Berkowitz 1990). If women with these conditions are chosen as controls, they would have a biased increase in HRT use compared to the general population. This in turn would reduce the ability to generalize the results to other women who were not affected with the same benign breast conditions and could reduce the validity of the study results. Therefore, the reduced relative risk found for HRT use and radiation exposure in the study population may be due to characteristic differences between cases and controls unrelated to breast cancer.

The advantage of using hospital controls in the study was that it ensured the same diagnostic criteria was used to classify cases and controls, eliminating the possibility of surveillance bias. Surveillance bias occurs when the type of diagnostic criteria used to classify patients is influenced by the exposure of interest (Hennekens 1987). For example, if HRT users were more likely to receive breast biopsies than nonusers, HRT users might have a greater chance of being diagnosed with breast cancer than nonusers. Using only biopsied cases and controls in the study eliminated this type of bias.

Another limitation of the study was the lack of certain types of information on the exposures of interest. With respect to HRT use, there was no information available on the dose of the hormone used. If this characteristic is an important factor in determining risk, it would have resulted in misclassification of exposure for some of the patients in the study. However, the lack of specific HRT dose information applied equally to cases and controls so that any misclassification that was introduced would have been nondifferential with respect to cases and controls. The overall effect would have been to make cases and controls appear to be more alike with respect to HRT exposure and to reduce the magnitude of the estimated risk of breast cancer from HRT use.

It is possible however, that there was little variation in the dose of HRT used by women in the study or that HRT dose is not a strong factor in determining risk. Hoover did not find a significant increase in the risk of breast cancer from high dose estrogen use (> 0.625 mg) therefore the effects of HRT dose on risk are inconclusive (Hoover 1976). Similarly, although no information was available on the regimen or mode of administration of replacement hormones by individual patients, there is no clear evidence that these are important risk determining factors. Hoover found that 'other than daily use' of estrogen was associated with a greater relative risk of breast cancer than 'daily use' of estrogen but again, the difference in risk was not statistically significant.

With respect to radiation exposure, there was a lack of information on the exact dose received outside of the study clinic by many of the study subjects. This required that the analysis be limited to those subjects that had only received clinic exposures or that had received exposure outside of the clinic that could be exactly determined.

Another limitation with respect to radiation exposure was the fact that most of the recorded exposures to patients were within ten years of the biopsy reference date. Many studies have suggested that the minimum latency period for the expression of breast cancer from radiation exposure is ten years (NRC 1990). Therefore, the exposures in this study may not have contributed to the risk of breast cancer because the majority of the exposures occurred within the expected latency period.

Notwithstanding this argument, it is possible that certain conditions such as hormone replacement therapy could modify the latency period of breast cancer from radiation exposure and some studies have suggested a reduced latency period with increasing age at exposure (NRC 1990). Latency periods shorter than ten years have been observed in some fluoroscopic studies (Mackenzie 1965, Sherman 1978) while latency periods greater than ten years were found in studies of women younger than age 60 or who were exposed to atomic bomb radiation (Boice 1978, Boice 1981, Shore 1986, NRC 1990).

Based on the variation in latency periods observed in past studies, no assumption was made regarding the minimum latency period of breast cancer from either radiation exposure or HRT use in the study. While this may have resulted in some exposure misclassification error by the inclusion of irrelevant exposures, it was a conservative approach in terms of risk assessment. Radiation exposures received within 12 months of the biopsy reference date were not included however, since most of these exposures were received as part of the reference biopsy. However, HRT exposure was included up to the date of the reference pathology report since the study was interested in the risk of breast cancer associated with current HRT use.

A major limitation of the study was the relatively small number of patients that could be used in the analysis. Although the original population included 24,450 female patients, after applying the eligibility criteria the study population was reduced to 252 cases and 342 controls. Of these, only 102 cases and 113 controls had a cumulative breast dose that could be determined accurately. This greatly reduced the ability to detect small differences in risk between various exposure and disease subgroups and in the end, reduced the power of the study to estimate risk within satisfactory confidence limits.

Most of the radiation risk confidence intervals included the null value of 1.0 resulting in a nonsignificant finding. The confidence intervals for the point estimates of relative risk at different levels of radiation dose had considerable overlap making it difficult to interpret trends in relative risk with dose. Although a the point estimates of risk increased monotonically from low dose to higher dose, this could have been due to chance given the large overlapping confidence intervals of the point estimates.

The preceding discussion also applies to the finding that mammographic radiation exposure and HRT use did not interact with one another to affect the risk of breast cancer. Modification of the risk of breast cancer by interaction between HRT and radiation may exist but the extent of the risk modification might depend on the amount of radiation exposure received. Most of the women in the study population had a cumulative breast dose less than 1,000 mrad from mammographic exposures which may not have been enough to detect interaction with HRT. Also, the small number of patients in the study reduced the power to detect subtle differences in HRT risk from interaction with mammographic radiation. The large, overlapping confidence intervals of the radiation strata shown in table 9 reflects the small sample size and illustrates the difficulty of detecting minimal changes in HRT risk between radiation subgroups.

Based on the information given in table 10, the odds ratio associated with unknown HRT use was equal to 2.29, indicating that cases were more than twice as likely as controls not to provide information on HRT use. If a non response was an indication of no HRT use, the odds ratio for HRT use would be even lower than was estimated. There is evidence to suggest that this may be the case since it has been suggested by Stanford (Stanford 1993, Stanford 1995) and shown by other investigators (Barrett-Conner 1991) that HRT users differ from nonusers in fundamental ways such as increased income level and education and perhaps a willingness or ability to respond to questionnaires.

C. Summary and Conclusions:

Ionizing radiation has been shown through studies of atomic bomb survivors and women exposed to large doses of medical x-rays to be a risk factor for breast cancer (NRC 1990). The relationship between breast cancer risk and dose appears to be linear in the moderate to high dose range and extrapolation of this risk has been used to estimate the risk of breast dose less than 50 rad (NRC 1990). The mechanism by which ionizing radiation causes breast cancer is probably through changes in the structure or expression of cellular genetic material leading to cells with a potential for unrestrained growth and proliferation (NRC 1990). It has been hypothesized that once these changes take place, certain agents may promote the full expression of cancer from a premalignant state to a metastatic condition.

Estrogen is suspected to be one of a number of agents which act as promoters of cancer (NRC 1990). Studies have been conducted of women using oral contraceptives and hormone replacement therapy to estimate the risk of cancer to the endometrium and breast and it appears that exogenous estrogen may be a risk factor for these diseases as well (Brinton 1993). The exact nature of the risk in terms of dose, duration of use and type of estrogen is somewhat unclear, however long term exposure to exogenous estrogens through hormone replacement therapy is suspected to increase the risk of breast cancer by 10 to 30 percent according to one meta-analysis (Steinberg 1991).

The objective of this study was to investigate the potential for interaction between ionizing radiation and hormone replacement therapy in modifying the risk of breast cancer from these agents. This was accomplished in a case-control study using 688 cases of breast cancer and 1,422 controls. The study utilized a population of women who had been examined and diagnosed for breast cancer at a breast imaging clinic in Edmonton, Alberta between 1989 and 1998. Women were chosen for the study if they were at least 60 years old at the time of diagnosis and had no prior personal history of breast cancer. In order to reduce the potential for selection bias and misclassification of disease in the study, only women who were diagnosed by histological examination of a biopsy sample were accepted for the study. This reduced the number of eligible study subjects to 215 cases of invasive breast cancer, 37 cases of in situ breast cancer and 342 controls from the original population of 24,420 potential study subjects.

Information on the study subjects was obtained by reviewing the charts located in the study clinic. The age and disease classification of each patient was obtained from a patient history form completed prior to the diagnosis at the clinic. Exposure histories were obtained exclusively from information in the patient chart as well. Information on hormone replacement therapy was obtained from the patient form and information on mammographic exposures was obtained from mammographic films and reports of previous mammograms on the patient history form.

The relative risk of breast cancer from mammographic radiation exposure and hormone replacement therapy was estimated by the odds ratio of exposure between cases and controls. A univariate logistic regression of the data was performed which identified risk factors that were important to the study population. Based on this information, important or significant variables were identified, and a multivariate logistic regression analysis was performed to determine the risk of breast cancer associated with each of the selected variables.

The results of the study did not demonstrate that cumulative breast dose, after adjustment for other factors, was associated with an increased risk of breast cancer in the study population over the range of dose studied (i.e. 1 - 3,400 mrad). Although an increase in the odds ratio was observed with increased dose, the confidence intervals of the point estimates of risk overlapped considerably, and the trend in risk was not considered to be evidence of a dose-response relationship.

Hormone replacement therapy also did not demonstrate a statistically significant association with an increased risk of breast cancer diagnosis in the study population (odds ratio = 0.55; 95% C.I. = 0.16 - 1.90) after adjustment for other factors. Although a stratified analysis based on hormone type showed a substantial difference in risk between current use of estrogen alone (odds ratio = 0.46; 95% C.I. = 0.01 - 2.37) and the risk for current use of estrogen-progestin (odds ratio = 1.69; 95% C.I. = 0.12 - 23.54), the confidence intervals overlapped considerably, and the point estimates of risk were not statistically significant.

When the analysis was stratified according to the type and stage of disease, substantial differences were found in the point estimates of risk for stage I and stage II breast cancer, however the confidence intervals overlapped and the point estimates were not statistically significant. Furthermore, the distribution of invasive tumour sizes was not found to be significantly different for women reporting current HRT use and women reporting no current HRT use. Therefore, the finding of a difference in risk of stage I and stage II breast cancer associated with current HRT use in the study population was probably a chance occurrence.

Finally, a test for interaction between HRT use and cumulative breast dose was performed by logistic regression and stratified analysis. In the logistic regression analysis, a term representing interaction between HRT and radiation dose was added to the model. A likelihood ratio test showed that the interaction term was not statistically significant ($p > 0.20$) and did not contribute to the logistic regression model for breast cancer. The stratified analysis also failed to find a significant interaction between HRT and radiation dose based on a chi-square test of homogeneity between the stratified odds ratios ($p > 0.20$). Therefore, there was no evidence that the risk of breast cancer in the study population was modified by interaction between hormone replacement therapy and cumulative breast dose.

In conclusion, this study did not find that mammograhic radiation exposure increased the chance of a malignant finding in women 60 years of age or older who had sufficient radiological indications for a biopsy. The study also found that women in the study group who reported current use of HRT were more likely to be diagnosed free invasive breast cancer than women who reported no current HRT use. Furthermore, the risk of a positive diagnosis of invasive breast cancer among women who received past mammographic radiation exposure in the study population did not appear to be modified by the history of current HRT use, after controlling for the possible confounding effects of age at biopsy, family cancer history, history of personal cancer, benign breast disease or type of menopause. However, these conclusions must be made with caution since the sample size of the study population was small, the range of breast dose in the study population was small, the information on past HRT use was limited and the possibility existed that uncontrolled confounding or selection bias may have affected the study results.

D. Future Work:

The results of this study raise certain questions for future research and may have practical implications as well. The finding that mammographic radiation exposure did not appear to increase the risk of breast cancer in this study population and may even be associated with a slight decrease in breast cancer risk should be further investigated. In particular, the possibility that frequent mammograms may result in the identification and treatment of benign lesions that are risk factors for breast cancer should be further investigated. To minimize the effect of statistical variation, a study requires a large number of subjects with complete exposure information on each subject. In this study, over 60 percent of the eligible patients received mammograms outside of the study clinic for which no exposure information was available. This greatly reduced the power of the study to detect changes in risk that were statistically significant. In order to overcome this problem in future studies, access to additional medical records, patient follow-up interviews and mammography history questionnaires will be required.

An additional shortcoming of the this study was the limited range of known dose in the study population for testing interaction with HRT. If more information had been available on exposures received outside of the study clinic, a larger range of dose might have been observed. Ultimately, the average lifetime mammographic dose for most women may not greatly exceed the dose range of this study. Therefore, for testing interaction with HRT, an alternate source of patients should be considered in future studies.

Finally, the the possibility that current HRT use may increase breast density or change parenchymal patterns and reduce mammographic sensitivity should be further investigated particularly if it results in diagnosis of breast cancer at a later stage of disease.

Tables

Table 1 Studies of Breast Cancer Risk Associated with Hormone Replacement.

no.	reference	date	type of study	type of control
1.	Hammond et al.	1979	prospective cohort	not applicable
2.	Colditz et al.	1990	prospective cohort	not applicable
3.	Gambrell et al.	1980	prospective cohort	not applicable
4.	Gambrell et al.	1983	prospective cohort	not applicable
5.	Buring et al.	1987	prospective cohort	not applicable
6.	Hunt et al.	1987	prospective cohort	not applicable
7.	Adami et al.	1989	prospective cohort	not applicable
8.	Bergkvist et al.	1989	prospective cohort	not applicable
9.	Mills et al.	1989	prospective cohort	not applicable
10.	Henderson et al.	1991	prospective cohort	not applicable
11.	Nachtigall et al.	1992	prospective cohort	not applicable
12.	Colditz et al.	1995	prospective cohort	not applicable
13.	Burch et al.	1974	retrospective cohort	not applicable
14.	Hoover et al.	1976	retrospective cohort	not applicable
15.	Bland et al.	1980	retrospective cohort	not applicable
16.	Thomas et al.	1982	retrospective cohort	not applicable
17.	Dupont et al.	1989	retrospective cohort	not applicable
18.	Risch et al.	1994	retrospective cohort	not applicable
19.	Sartwell et al.	1977	case-control	hospital
20.	Wynder et al.	1978	case-control	hospital
21.	Ravinhar et al.	1979	case-control	hospital
22.	Jick et al.	1980	case-control	hospital
23.	Ross et al.	1980	case-control	community
24.	Brinton et al.	1981	case-control	community
25.	Hoover et al.	1981	case-control	community
26.	Hoover et al.	1981	case-control	community
27.	Kelsey et al.	1981	case-control	hospital
28.	Hulka et al.	1982	case-control	both
29.	Sherman et al.	1983	case-control	hospital
30.	Hiatt et al.	1984	case-control	community
31.	Horwitz et al.	1984	case-control	hospital
32.	Kaufman et al.	1984	case-control	hospital
33.	Brinton et al.	1986	case-control	community
34.	La Vecchia et al.	1986	case-control	hospital
35.	Nomura et al.	1986	case-control	both
36.	Wingo et al.	1987	case-control	community
37.	Brownson et al.	1988	case-control	community
38.	Ewertz et al.	1988	case-control	community
39.	Rohan et al.	1988	case-control	community
40.	Kaufman et al.	1991	case-control	hospital
41.	Palmer et al.	1991	case-control	community
42.	Harris et al.	1992	case-control	hospital
43.	Stanford et al.	1995	case-control	community
44.	Nachtigall et al.	1992	clinical trial	hospital
45.	Armstrong	1988	meta-analysis	not applicable
46.	Dupont et al.	1991	meta-analysis	not applicable
47.	Steinberg et al.	1991	meta-analysis	not applicable
48.	Heinrich	1992	meta-analysis	not applicable
49.	Sillero-Arenas et al.	1992	meta-analysis	not applicable
50.	Steinberg	1994	meta-analysis	not applicable

Table 2 Relative Risk of Breast Cancer Associated with Hormone Replacement Therapy Estimated By Different Diagnostic Methods and Types of Controls. †

diagnostic method	type of control	relative risk	95% confidence interval
mammography	women with benign breast disease	0.4	0.3 - 0.7
biopsy	biopsied women only	0.8	0.5 - 1.4
all methods	women with other medical conditions		
	- indeterminate exposure included	0.9	0.5 - 1.7
	- indeterminate exposures excluded	3.3	2.2 - 5.0

† From Horocks 1994

Table 3 Relative Risk of Breast Cancer Associated With Hormone Replacement Therapy (meta-analysis results from this study).

	Relative Risk (95% Confidence Interval)		
hormone	**ever use**	**≤ 9 years**	**> 9 years**
all estrogens	1.04 (.99, 1.09)	1.00 (.95, 1.05)	0.92 (.83, 1.03)
conjugated estrogen	0.99 (.95, 1.04)	0.99 (.94, 1.04)	0.91 (.82, 1.02)
synthetic estrogen	1.21 (1.1, 1.32)	1.07 (.91, 1.26)	1.52 (1.13, 2.03)
estrogen-progestin	1.23 (1.06, 1.42)	0.88 (.68, 1.16)	4.40 (.9, 22.40)
estrogen-androgen	2.18 (1.36, 3.49)	insufficient data	insufficient data
progestin alone	1.36 (.91, 2.02)	insufficient data	insufficient data

Table 4 General Format of Contingency Table Used in the Study

Exposure	Cases	Controls
Yes	a	b
No	c	d
Total	a + c	b + d

Table 5 Percentage of Selected Characteristics Among Invasive Breast Cancer Cases and Controls.

characteristic	cases (n = 215) %	controls (n = 342) %
age at biopsy, years		
60 - 64	24.7	29.2
65 - 69	28.8	32.2
70 - 74	20.5	20.2
≥ 75	26.0	18.4
age at menarche, years		
< 12	13.0	13.5
12 - 14	53.1	57.6
> 14	16.7	16.1
unknown	17.2	12.9
parity (n)		
0	10.7	10.8
1 or 2	25.6	28.7
≥ 3	57.2	56.7
unknown	6.5	3.8
prior hysterectomy	38.1	38.6
bilateral ovariectomy	13.0	20.2
family history of breast cancer	27.9	23.1
family history of cancer (non-breast)	26.1	24.6
prior cancer (non-breast)	8.4	5.0
history of benign breast disease	10.7	12.9
current prescription medication	61.4	69.9
current hormone replacement therapy	22.3	34.5
past mammographic radiation exposure	71.0	83.9

Table 6 Distribution of HRT Duration Among Breast Cancer Cases and Controls.

		Current HRT Duration (months)				
group	**n**	**min**	**max**	**mean**	**t**[†]	**p**
controls	313	0	516	51.8	reference	
cases						
in situ	34	0	360	67.4	0.76	> 0.10
invasive	184	0	396	33.3	2.21	< 0.05

[†] t test of difference between mean value of cases and controls

Table 7 Distribution of Cumulative Breast Dose Among Breast Cancer Cases and Controls.

		Cumulative Breast Dose (mrad)				
group	**n**	**min**	**max**	**mean**	**t** †	**p**
cases	102	0	2988	344		
controls	113	0	3352	423	1.12	> 0.25

† two tailed t-test of difference in mean values between cases and controls

Table 8 Code for the Study Variables.

variable	abbreviation
index number	IDX
age at biopsy (years)	AGE
diagnosis (0 = benign, 1 = invasive, 2 = in situ only)	DIA
diameter of invasive breast tumour (cm)	CM
stage of invasive breast cancer (0 = na, 1 = stage I, 2 = stage II, 3 = no information	STG
current hormone replacement therapy (0 = no, 1 = yes, 2 = no information)	HRT
months of current hormone replacement therapy (0 = none, 1 = 1 to 120, 2 = 121 to 240, 3 = 240 to 360, 4 = no information)	DUR
type of hormone replacement therapy (0 = none, 1 = estrogen only, 2 = estrogen-progestin, 3 = no information)	TYP
cumulative breast dose in mrad (0 = zero, 1 = 1 to 400, 2 = 401 to 800, 3 = 801 to 1200, 4 = 1201 to 1600, 5 = 1601 or greater, 6 = unknown)	DOS
age at menarche in years (0 = less than 12, 1 = 12 to 14, 2 = 14 or greater, 3 = no information)	MEN
number of live births (0 = none, 1 = 1 or 2, 2 = 3 or more, 3 = no information)	PAR
prior hysterectomy (0 = no, 1 = yes, 2 = no information)	HYS
prior ovariectomy (0 = no, 1 = unilateral, 2 = bilateral, 3 = no information)	OVR
prior family breast cancer (0 = no, 1 = yes, 2 = no information)	FBC
prior family cancer - nonbreast (0 = no, 1 = yes, 2 = no information)	FCA
prior personal cancer - nonbreast (0 = no, 1 = yes, 2 = no information)	PCA
prior benign breast disease (0 = no, 1 = yes, 2 = no information)	BBD

Table 9 Univariate Logistic Regression Models for Invasive Breast Cancer.

code	stratum	β	SE (B)	odds ratio	95% C.I.	n	p
AGE		0.0270	0.0133	1.31 †	1.01 - 1.70	557	0.04
MEN	(0)	reference		1.0	reference	74	
	(1)	- 0.0506	0.2670	0.95	0.56 - 1.60	311	0.85
	(2)	0.0726	0.3216	1.08	0.58 - 2.03	91	0.82
	(3)	0.3232	0.3274	1.38	0.73 - 2.62	81	0.32
PAR	(0)	reference		1.0	reference	60	
	(1)	- 0.1022	0.3145	0.90	0.49 - 1.67	153	0.75
	(2)	0.0197	0.2895	1.02	0.58 - 1.80	317	0.95
	(3)	0.5495	0.4678	1.73	0.69 - 4.33	27	0.24
HYS	(0)	reference		1.0	reference	326	
	(1)	- 0.0398	0.1806	0.96	0.67 - 1.37	214	0.83
	(2)	- 0.4387	0.5442	0.65	0.22 - 1.89	17	0.42
OVR	(0)	reference		1.0	reference	334	
	(1)	- 0.2320	0.3643	0.79	0.39 - 1.61	36	0.52
	(2)	- 0.5627	0.2500	0.57	0.35 - 0.93	97	0.02
	(3)	- 0.1135	0.2431	0.89	0.55 - 1.43	90	0.64
FBC	(0)	reference		1.0	reference	349	
	(1)	0.3207	0.2045	1.38	0.92 - 2.06	139	0.12
	(2)	0.3922	0.2666	1.48	0.88 - 2.50	69	0.14
FCA	(0)	reference		1.0	reference	308	
	(1)	0.2107	0.2098	1.23	0.81 - 1.86	140	0.32
	(2)	0.4875	0.2261	1.63	1.05 - 2.54	109	0.03
PCA	(0)	reference		1.0	reference	440	
	(1)	0.6266	0.3525	1.87	0.94 - 3.73	35	0.08
	(2)	0.4228	0.2427	1.53	0.67 - 3.50	82	0.08
BBD	(0)	reference		1.0	reference	413	
	(1)	- 0.1700	0.2765	0.84	0.49 - 1.44	67	0.54
	(2)	0.2438	0.2508	1.28	0.78 - 2.09	77	0.33
HRT	(0)	reference		1.0	reference	343	
	(1)	- 0.5037	0.2035	0.60	0.40 - 0.89	166	0.01
	(2)	0.8186	0.3150	2.27	1.22 - 4.21	48	0.01
DUR	(0)	reference		1.0	reference	344	
	(1)	- 0.4644	0.2670	0.63	0.37 - 1.06	81	0.08
	(2)	- 0.2002	0.3212	0.82	0.44 - 1.54	48	0.53
	(3)	- 0.9344	0.5145	0.39	0.14 - 1.07	24	0.07
	(4)	0.4673	0.2808	1.60	0.92 - 2.77	60	0.10
DOS	(0)	reference		1.0	reference	63	
	(1)	- 0.6687	0.3390	0.51	0.26 - 0.99	83	0.05
	(2)	- 0.5892	0.4299	0.55	0.24 - 1.28	34	0.17
	(3)	- 0.5199	0.4830	0.59	0.23 - 1.52	24	0.28
	(4)	- 0.3528	1.0322	0.70	0.09 - 5.29	4	0.73
	(5)	- 1.2684	0.8748	0.28	0.05 - 1.55	7	0.15
	(6)	-1.0590	0.2805	0.35	0.20 - 0.61	342	0.00

† odds ratio is for a ten year increase in age treated as a continuous variable

Table 10 Multivariate Model Containing Biologically Important Variables or Variables Identified as Significant in the Univariate Analysis.

code	stratum	β	SE (B)	odds ratio	95% C.I.	n
AGE	continuous	0.0133	0.0232	1.14 †	0.73 - 1.80	215
OVR	no	reference		1.00	reference	121
	unilateral	- 0.0974	0.6622	0.91	0.25 - 3.32	14
	bilateral	- 0.3332	0.4743	0.72	0.28 - 1.82	32
	unknown	- 0.7207	0.3959	0.49	0.22 - 1.06	48
FBC	no	reference		1.00	reference	126
	yes	0.0454	0.3754	1.05	0.50 - 2.18	57
	unknown	- 0.2740	0.4860	0.76	0.29 - 1.97	32
FCA	no	reference		1.00	reference	123
	yes	0.0595	0.3853	1.06	0.50 - 2.26	49
	unknown	1.1828	0.4538	3.26	1.34 - 7.94	43
PCA	no	reference		1.00	reference	160
	yes	1.8120	0.8776	6.12	1.10 - 34.20	11
	unknown	0.2048	0.6940	1.23	0.32 - 4.78	44
BBD	no	reference		1.00	reference	152
	yes	0.3134	0.5075	1.37	0.51 - 3.70	24
	unknown	0.2520	0.7275	1.29	0.31 - 5.35	39
HRT	no	reference		1.00	reference	139
	yes	- 0.6211	0.3583	0.54	0.27 - 1.10	60
	unknown	1.0025	0.6596	2.73	0.75 - 9.93	16
DOS	0 mrad	reference		1.00	reference	63
	1 - 400	- 0.4429	0.3889	0.64	0.30 -1.38	83
	401 - 800	- 0.4357	0.4907	0.65	0.25 - 1.69	34
	801 - 1200	- 0.0964	0.5421	0.91	0.31 - 2.63	24
	1201 - 1600	0.1238	1.1241	1.13	0.13 - 10.25	4
	> 1600	- 1.3120	0.9777	0.27	0.04 - 1.83	7
Constant		- 0.3743	1.0828			

† odds ratio is for a ten year increase in age treated as a continuous variable

Table 11 Log-likelihood Ratio Test Statistic for the Addition of Interaction Terms to the Multivariate Model.

modification	log-likelihood	G	df	significance
main effects only †	262.682			
add AGE x OVR	259.385	3.297	3	0.80 > p > 0.20
add AGE x FBC	262.360	0.322	2	0.90 > p > 0.80
add AGE x FCA	262.133	0.549	2	0.80 > p > 0.20
add AGE x PCA	261.600	1.082	2	0.80 > p > 0.20
add AGE x BBD	260.998	1.684	2	0.80 > p > 0.20
add AGE x HRT	262.510	0.172	2	0.95 > p > 0.90
add AGE x DOS	251.876	10.806	5	0.10 > p > 0.05
add OVR x FBC	260.238	2.444	6	0.90 > p > 0.80
add OVR x FCA	256.270	6.412	6	0.80 > p > 0.20
add OVR x PCA	257.464	5.218	5	0.80 > p > 0.20
add OVR x BBD	255.963	6.719	6	0.80 > p > 0.20
add OVR x HRT	246.517	16.165	6	0.02 > p > 0.01
add OVR x DOS	245.180	17.502	13	0.20 > p > 0.10
add FBC x FCA	257.333	5.349	4	0.80 > p > 0.20
add FBC x PCA	259.866	2.816	4	0.80 > p > 0.20
add FBC x BBD	256.602	6.080	4	0.20 > p > 0.10
add FBC x HRT	260.368	2.314	4	0.80 > p > 0.20
add FBC x DOS	257.041	5.641	7	0.80 > p > 0.20
add FCA x PCA	261.018	1.664	4	0.80 > p > 0.20
add FCA x BBD	262.189	0.493	3	0.95 > p > 0.90
add FCA x HRT	251.747	10.935	4	0.05 > p > 0.02
add FCA x DOS	245.333	17.349	10	0.10 > p > 0.05
add PCA x BBD	256.110	6.572	3	0.10 > p > 0.05
add PCA x HRT	258.498	4.184	3	0.80 > p > 0.20
add PCA x DOS	255.118	7.564	9	0.80 > p > 0.20
add BBD x HRT	262.187	0.495	3	0.95 > p > 0.90
add BBD x DOS	253.391	9.291	10	0.80 > p > 0.20
add HRT x DOS	256.708	5.974	7	0.80 > p > 0.20

† includes AGE, OVR, FBC, FCA, PCA, BBD, HRT and DOS

Table 12 Relative Risk of Invasive Breast Cancer Associated with Current HRT Use of Any Duration. (stratified by cumulative mammographic radiation dose)

cumulative breast dose (mrad)	HRT use	cases (n)	controls (n)	odds ratio	95% C.I.
0	yes	6	6		
	no	23	19	0.83	0.23 - 2.98
1 - 800	yes	11	27		
	no	35	37	0.43	0.19 - 0.99
> 800	yes	4	6		
	no	11	14	0.85	0.19 - 3.78

chi-square test of homogeneity = 1.041

p > 0.50

Table 13 Relative Risk of Invasive Breast Cancer Associated with Mammographic Radiation Dose (stratified by HRT use)

HRT use	cumulative breast dose (mrad)	cases (n)	controls (n)	odds ratio	95% C.I.
no	0	23	19		
	1 - 3400	56	60	0.77	0.38 - 1.56
yes	0	6	6		
	1 - 3400	15	33	0.45	0.12 - 1.63

chi-square test of homogeneity = 0.516

$p > 0.20$

Table 14 Multivariate Model With Significant Interaction Terms (OVR*HRT and FCA*HRT) Included

code	stratum	β	SE (B)	odds ratio	95% C.I.	n
AGE	continuous	0.018	0.050	1.20 †	0.45 -3.19	215
OVR	no	reference		1.00	reference	121
	unilateral	0.0994	0.8497	1.11	0.21 - 5.84	14
	bilateral	- 0.2508	0.6858	0.78	0.20 - 2.98	32
	unknown	0.1371	0.4637	1.15	0.46 - 2.85	48
FBC	no	reference		1.00	reference	126
	yes	0.3418	0.4243	1.41	0.61 - 3.23	57
	unknown	- 0.2767	0.5397	0.76	0.26 - 2.18	32
FCA	no	reference		1.00	reference	123
	yes	0.1431	0.4518	1.15	0.48 - 2.80	49
	unknown	0.1230	0.5583	1.13	0.34 - 3.38	43
PCA	no	reference		1.00	reference	160
	yes	2.3650	0.9725	10.64	1.58 - 71.6	11
	unknown	1.3217	1.0262	3.75	0.50 - 28.02	44
BBD	no	reference		1.00	reference	152
	yes	0.1074	0.5429	1.11	0.38 - 3.23	24
	unknown	- 0.7745	1.0502	0.46	0.06 - 3.61	39
HRT	no	reference		1.00	reference	139
	yes	- 0.6060	0.6365	0.55	0.16 - 1.90	60
	unknown	9.7533	56.5653	17,210.93	E-44 - E-52	16
DOS	0 mrad	reference		1.00	reference	63
	1 - 400	- 0.1092	0.4283	0.90	0.40 - 2.08	83
	401- 800	- 0.1548	0.5224	0.86	0.31 - 2.39	34
	801 - 1200	- 0.2130	0.5822	0.81	0.26 - 2.53	24
	1201 - 1600	0.9204	1.3631	2.51	0.17 - 36.31	4
	>1600	- 2.3522	1.2702	0.10	0.01 - 1.15	7

† odds ratio is for a ten year increase in age treated as a continuous variable

Table 15 Relative Risk of Invasive Breast Cancer Stratified by HRT Type (adjusted for AGE, OVR, FBC, FCA, PCA, BBD, DOS and interaction terms)

Current HRT	β	SE (B)	odds ratio	95% C.I.	n
none	reference		1.00	reference	139
estrogen only	- 0.7799	0.8386	0.46	0.01 - 2.37	41
estogen-progestin	0.5231	1.3446	1.69	0.12 - 23.54	8

Table 16 Relative Risk of Breast Cancer Stratified by HRT Type and Stage of Disease (adjusted for AGE, OVR, FBC, FCA, PCA, BBD, DOS and interaction terms)

Type of Breast Cancer	β	SE (B)	odds ratio	95% C.I.	n
In situ					
No HRT use	reference		1.00	reference	77
HRT use	1.6262	1.9688	5.09	0.11 - 241.06	41
Stage I invasive (negative lymph nodes)					
No HRT use	reference		1.00	reference	123
HRT use	- 1.4976	0.8997	0.22	0.04 - 1.30	51
Stage II invasive (positive lymph nodes)					
No HRT	reference		1.00	reference	79
HRT use	0.3330	1.9693	1.40	0.03 - 66.21	44

Table 17 Relative Risk of Invasive Breast Cancer Associated with Current HRT Use Stratified by Tumour Size (adjusted for AGE, OVR, FBC, FCA, PCA, BBD, DOS and interactions terms)

tumour size (cm)	β	SE (B)	odds ratio	95% C.I.	n
0.1 - 1.0					
No HRT	reference		1.00	reference	94
HRT use	- 3.0422	1.6353	0.05	0.00 - 1.18	45
1.1 - 2.0					
No HRT	reference		1.00	reference	97
HRT use	- 1.0289	1.1959	0.36	0.03 - 3.73	46
2.1 - 3.0					
No HRT	reference		1.00	reference	75
HRT use	- 0.0065	1.7768	0.99	0.03 - 32.33	41
> 3.0					
No HRT	reference		1.00	reference	73
HRT use	- 9.4654	166.2074	insufficient data		40

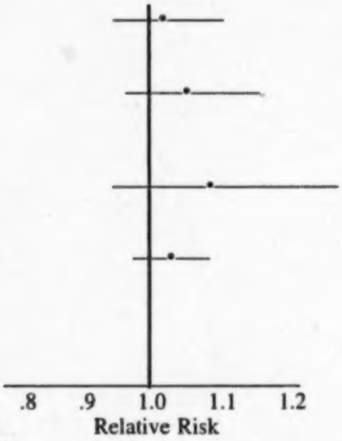
Table 18 Invasive Tumour Size Distribution Among Current Users and Nonusers of HRT.

		Tumour Size (cm)				
stage	**HRT use**	**min**	**max**	**mean**	**significance †**	**p**
all	yes	0.44	4.00	1.55		
	no	0.30	10.00	1.58		
I	yes	0.40	4.00	1.51		
	no	0.20	5.00	1.37	1.30	> 0.10
II	yes	0.40	4.00	1.77		
	no	1.00	10.00	2.63	1.587	>0.10

† t test of difference between mean tumour sizes.

Figures

Figure 1 Mean Relative Risk of Breast Cancer for 'Ever Use' Hormone Replacement Therapy from Meta-Analysis



Study Type included	RR	C.I.	Studies
cohort	1.02	0.96 to 1.09	4,5,6,7,9,10 15,17.18
case-control	1.05	0.98 to 1.13	19,24,27,30 33,34,36,37 38,39,40,41 43
hospital control	1.08	0.94 to 1.24	19,27,34,40
community control	1.03	0.98 to 1.08	24,30,33,36 37,38,39,41 43

Figure 2 **Study Population**

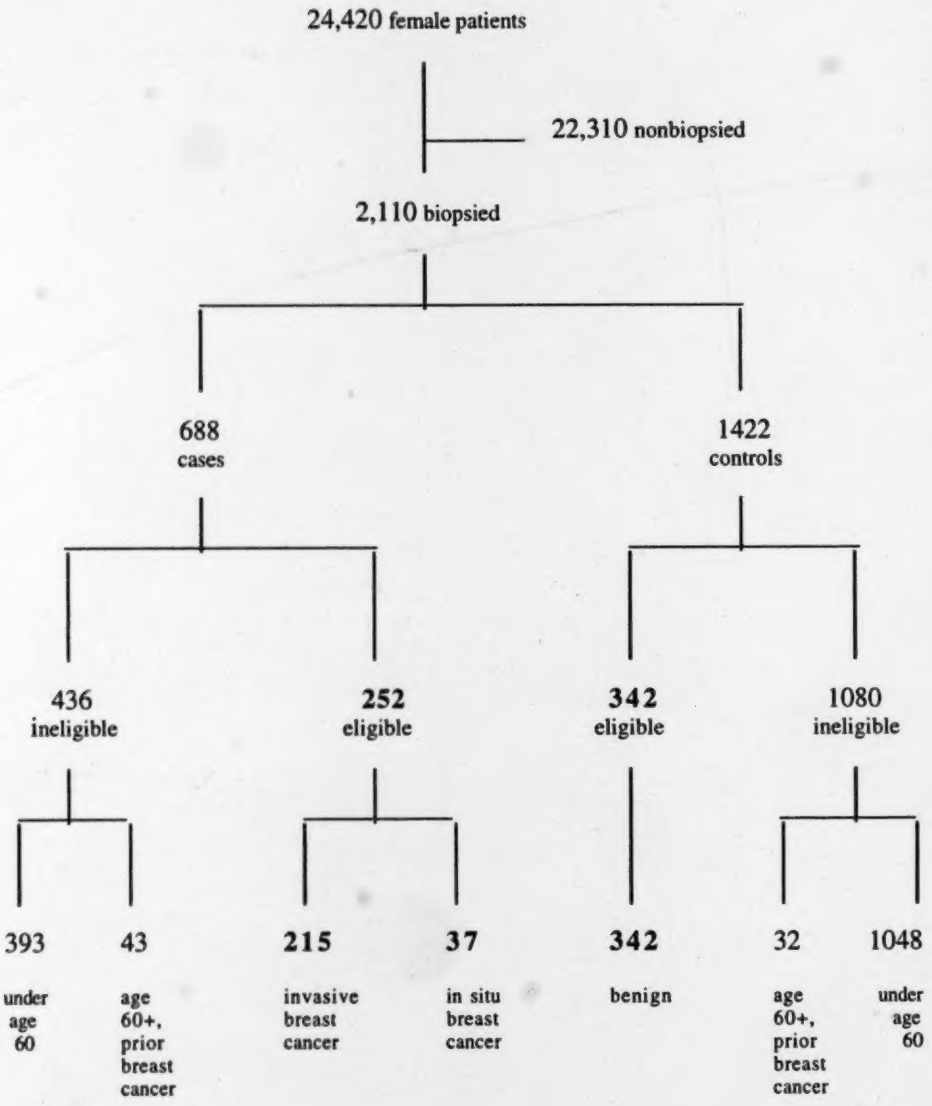

24,420 female patients
22,310 nonbiopsied
2,110 biopsied
688 cases
1422 controls
436 ineligible
252 eligible
342 eligible
1080 ineligible
393 under age 60
43 age 60+, prior breast cancer
215 invasive breast cancer
37 in situ breast cancer
342 benign
32 age 60+, prior breast cancer
1048 under age 60

Figure 3 **Patient History Form**

PATIENT HISTORY

Please take a moment and fill out this patient history sheet. Leave anything that doesn't apply. THANK YOU.

NAME: ______________________________ Date: ________________
Last First

Chart #: ________________

DATE OF BIRTH: ____/____/19____

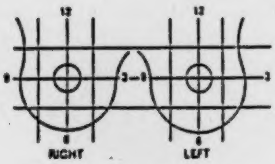
Previous Mammogram: NO YES Where? ______________ When? __________
(Circle)

MENSTRUAL HISTORY

Approximate age of very first period ? ______ First day of last menstrual period? ______________
Number of pregnancies? ______ Number of live births? ______ How many were breast fed? ______
Have you had a hysterectomy? NO YES When? ______________
Ovaries removed? NO ONE BOTH

CURRENT SYMPTOMS THAT APPLY TO YOURSELF: (Circle) NONE

Skin or nipple changes......... (ie. dimpling / inversion)	RT	LT	How long? ______
Nipple discharge..................	RT	LT	How long? ______ Color ______
Lump..................................	RT	LT	How long? ______
Pain or discomfort................	RT	LT	How long? ______



Please indicate problem(s) with an "X".

PERSONAL BREAST HISTORY:

Cysts drained?	RT	LT	
Breast Surgery?	RT	LT	When? __________
Recent Injury?	RT	LT	When? __________

Personal history of breast cancer or other cancers: ______________________________

MEDICATIONS:

Hormones ________ How long? ________ / Birth control pills ________ How long? ________
(ie. Premarin / Provera / Estrogen)
Other prescription medication? Please specify: ______________________________
Any recent changes in medications? Please specify: ______________________________

BREAST CANCER HISTORY THAT APPLIES TO YOUR FAMILY: (Circle)

Blood relatives with a history of breast cancer? NO YES NONE UNKNOWN

AGE of diagnosis: MOTHER ____ SISTER(S) ____ DAUGHTER(S) ____
GRANDMOTHERS - MATERNAL ____ PATERNAL ____ OTHER ________
(Mother) (Father)

IMMEDIATE RELATIVES WITH A HISTORY OF CANCER:

Cervical cancer	______________	Uterine cancer	______________
Ovarian cancer	______________	Colon cancer	______________
Malignant Melanoma (mole)	______________	Prostate cancer	______________

Figure 4 **Radiology Report**

STEREOTACTIC
PATIENT DATA SHEET

Name:____________ ID#__________ Exam Date:__________
Address:______________________________
Telephone: Residence:__________ Business:__________ DOB:__________
Referring Physician:____________________ Clinic:__________
Telephone:__________ Fax:__________ Referral Request Received:______

Imaging Examinations: **PATIENT HISTORY**
Mammogram: Date:______ Place:__________ Dx:______________
Date:______ Place:__________ Dx:______________
Ultrasound: Date:______ Place:__________ Dx:______________
Breast Biopsies: Date:______ Place:__________ Dx:______________
Date:______ Place:__________ Dx:______________
Breast Surgery: Date:______ Place:__________ Procedure:__________
Family History:______________________________
Current Medications:______________________________
Relevant Medical History:______________________________

EXAMINATION NOTES Procedure Physician:______________
Indication for Biopsy:______________________________
Recommended by: Radiologist:__________ Surgeon:__________ Other:__________
Area of Concern: Palpable:______________ Non-Palpable:______________
Calcifications: Yes:_____ No:_____ Mass: Yes:_____ No:_____ Both: Yes:_____ No:_____
Architectural Distortion: Yes:_____ No:_____ Other:______________
Size: 1-5 mm_____ 6-10 mm_____ 11-15 mm_____ 16-20 mm_____ 20 + mm_____
Pre-Biopsy Suspicion: High:__________ Intermediate:__________ Low:__________
# Cores Removed:______ Calcifications Confirmed in Cores: Yes:_____ No:_____ N.A._____
Pathological Dx: Benign:__________ Atypia:__________ Malignant:__________
____
Surgery: Bx: _____ Wedge: _____ Mastectomy:_____ Congruence with LCNB: Yes:_____ No:_____
____

EXAMINATION FOLLOW-UP CHECKLIST
Procedure Report Dictated:__________ Pathology Report Received:__________
Correspondence: Referring Physician: Phone:______ Letter:______ Patient: Phone:______
Follow-up Mammogram Date:______________ Completed: Yes:______ No:______
Additional Mammography Follow-up Required:______ Details:______________
Repeat LCNB: Yes______ No:______ Surgical Biopsy Recommended: Yes:______ No:______
Congruence With Original LCNB Pathology: Yes:_____ No:_____
____
Additional Notes:______________________________
____

Figure 5

SURGICAL PATHOLOGY REPORT

PATIENT: LOC / RM #
ID # (PHN): PHYS:
AGE: SEX: DOB:
CHART / PH #:
MED. REC. #:
POSTAL CODE: COPY:

COLLECT DATE: ACCESSION #:

RECEIVED DATE:

CLINICAL HISTORY:

INTRAOPERATIVE DIAGNOSIS:

MICROSCOPIC DESCRIPTION:

DIAGNOSIS:

Pathologist:

PATIENT: END OF REPORT
ACC #: PHN #: PAGE:

Figure 5

SURGICAL PATHOLOGY REPORT
(continued)

SUMMARY OF REPORT OF CARCINOMA OF THE BREAST (Recommendations)

SPECIMEN SIZE:

INVASIVE CARCINOMA:
HISTO TYPE (S):
SIZE:
GRADE: NUCLEAR SCORE /3 MITOTIC SCORE /3 TUBULAR SCORE /3
HISTOLOGIC GRADE /3
LYMPHATIC / VASCULAR INVASION:
MARGINS:
HORMONE RECEPTORS: PARAFFIN BLOCK:
SKIN: NIPPLE: SKELETAL MUSCLE:
DCIS?: DISTANCE BEYOND INVASION:

DUCTAL CARCINOMA IN SITU (DCIS):
SIZE: NUMBER OF SLIDES INVOLVED:
MARGINS COAGULATION NECROSIS: /3
PATTERN (S): PAGET'S DISEASE:

LYMPH NODES:
NUMBERS: NUMBER POSITIVE:
LARGEST METASTATIS: EXTRANODAL INVASION:
EXTRANODAL LYMPHATIC / VASCULAR:

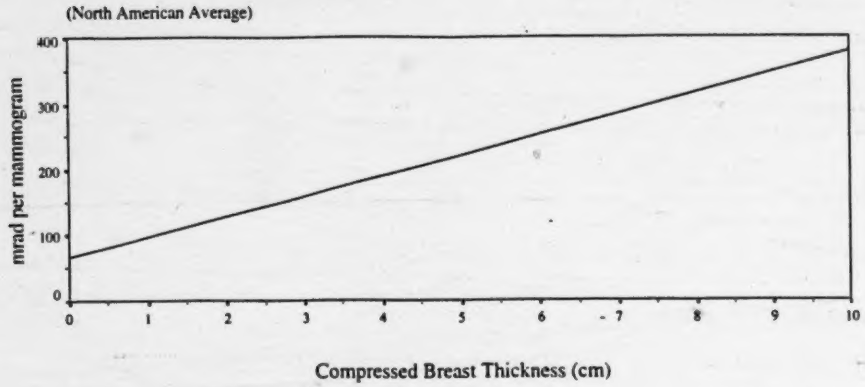
OTHER ABNORMALITIES:
LOBULAR CARCINOMA IN SITU (LCIS):
CALCIFICATIONS AND LOCATION:
OTHER PROLIFERATIVE ABNORMALITIES:

Figure 6 **Patient Data Summary Form**

1. Sequence number (1- 2000) ____________________
2. Sex (f/m) ____________________
3. Date-of-birth (yr/mo) ____________________
4. Patient questionnaire date (yr/mo) ____________________
5. Age at menarche (year/?/nr) ____________________
6. Parity (number/nr) ____________________
7. Hysterectomy (y/n/?/nr) ____________________
8. Ovariectomy (uni/bi/n/?/nr) ____________________
9. HRT use (y/n/nr) ____________________
10. HRT duration (mos/na/nr) ____________________
11. HRT type (name/na/?/nr) ____________________
12. Other prescriptions (y/n/?/nr) ____________________
13. Fam breast ca (y/n/?/nr) ____________________
14. Fam non-breast ca (type/n/?/nr) ____________________
15. Personal non-breast ca (type/n/nr) ____________________

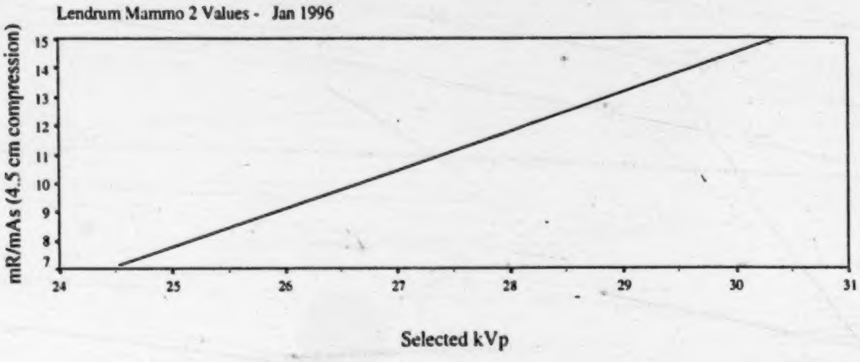
	Right Breast	Left Breast
16. Current breast symptoms (y/n/nr)		
17. Duration of symptoms (mos/na/?/nr)		
18. Benign breast disease (y/n/?/nr)		
19. Prior breast cancer (y/n/?/nr)		
20. Ref path report date (yr/mo)		
21. Age-at-biopsy (yrs/mos)		
22. Diagnosis (iv/is/b)		
23. Tumour size (cm/?/na)		
24. Breast ca stage (I/II/?/na)		
25. Mammogram location (c/o)		
26. Mammogram date (yr/mo/?)		
27. Mammogram voltage (kVp/ ?)		
28. Mammogram current (mAs/?)		
29. Mammogram CBT (cm/?)		
30. Mean glandular breast dose (mrad)		
31. Cumulative breast dose (mrad/?)		

Figure 7 Breast Dose versus Compressed Breast Thickness



Reference - Gentry 1996

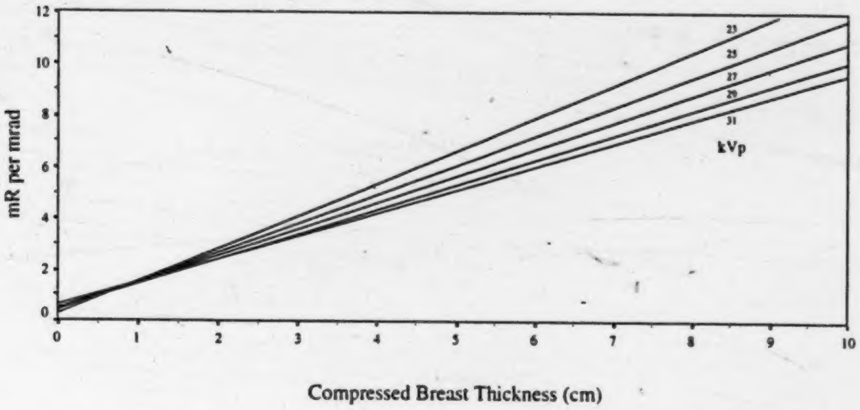
Figure 8 Entrance Skin Exposure versus X-Ray Machine Settings



Courtesy of:

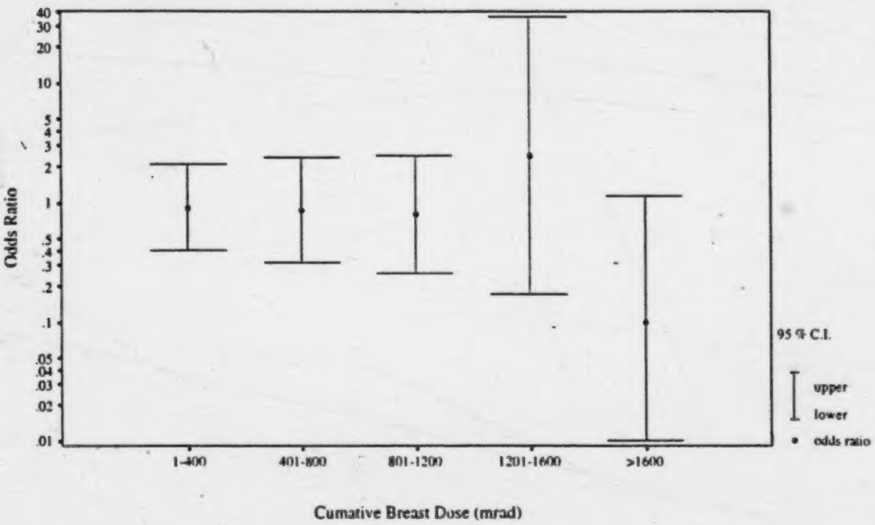
Radiation Physics Consultants

Figure 9 Exposure-Dose Ratio versus Compressed Breast Thickness



Reference - Wu 1991

Figure 10 Relative Risk of Invasive Breast Cancer Associated with Cumulative Breast Dose



References

Adami, H.O.; Persson, I.; Hoover, R.; et al. Risk of cancer in women receiving hormone replacement therapy. Int J Cancer. 44:833; 1989.

Armstrong, B.K. Oestrogen therapy after menopause - boon or bane? Med J Aus. 148:21; 1988.

Ballard-Barbash, R; Schatzkin, A.; Carter, C.L.; et al. Body fat distribution and breast cancer in the Framingham study. J Natl Cancer Inst. 82 (4): 286; 1990.

Barral, E.; Larsson, L.E.; Mattsson, B.; et al. Breast cancer following irradiation of the breast. Cancer. 40:2905; 1977.

Barrett-Conner, E. Postmenopausal estrogen and prevention bias. Ann Int Med. 115:455; 1991.

Barton, S.A.; Pathak, D.R.; Black, W.C.; et al. Prevalence of benign, atypical, and malignant breast lesions in populations at different risk for breast cancer. Cancer. 60:2751; 1987.

Baum, M.; Saunders, C.; Meredith, S. Breast Cancer. A guide for every woman. Oxford University Press. New York. 1994.

Bergkvist, L.; Adami, H.O.; Persson, I.; et al. The risk of breast cancer after estrogen and estrogen-progestin replacement. N Engl J Med. 321:293; 1989.

Berkowitz, J.E.; Gatewood, O.M.B.; Goldblum, L.E.; Hormonal replacement therapy: Mammographic manifestations. Radiology. 174:199; 1990.

Bland, K.I.; Buchanan, J.B.; Weisberg, B.F.; et al. The effects of exogenous estrogen replacement therapy of the breast. Cancer. 45:3027; 1980.

Boice, J.D. Jr.; Monson, R.R. Breast cancer in women after repeated fluoroscopic examinations of the chest. J Natl Cancer Inst. 59:823; 1977.

Boice, J.D. Jr.; Rosenthal, M.; Trout, E.D. Estimation of breast doses and breast cancer risk associated with repeated fluoroscopic chest examinations of women with tuberculosis. Radiat Res. 73:373; 1978.

Boice, J.D.; Stone, B.J. Interaction between radiation and other breast cancer risk factors. In: Late Biological Effects of Ionizing Radiation, Vol. 1, pp 231 to 249, Proceedings of a Symposium, International Atomic Energy Agency, Vienna; 1978.

Boice, J.D.; Monson, R.R.; Rosenstein, M.; et al. Cancer mortality in women after repeated fluoroscopic examinations of the chest. J Natl Cancer Inst. 66:863; 1981.

Boice, J.D.; Blettner, M.; Kleinerman, R.A.; et al. Radiation dose and breast cancer risk in patients treated for cancer of the cervix. Int J Cancer. 44:7; 1989.

Boice, J.D.; Preston, D.; Davis, F.G.; et al. Frequent chest x-ray fluoroscopy and breast cancer incidence among tuberculosis patients in Massachusetts. Radiat Res. 125:214; 1991.

Bond, V.P.; Cronkite, E.P.; Lippencott, S.W.; et al. Studies on radiation - induced mammary gland neoplasms in the rat. III. Relation of the neoplastic response to dose of total radiation. Radiat Res. 12:276; 1960.

Brinton, L.A.; Hoover, R.N.; Szklo, M.; Menopausal estrogen use and risk of breast cancer. Cancer. 47:2517; 1981.

Brinton, L.A.; Hoover, R.; Fraumeni, J.F. Jr. Menopausal oestrogens and breast cancer risk: An expanded case-control study. Br J Cancer. 54:825; 1986.

Brinton, L.A.; Schairer, C. Estrogen replacement therapy and breast cancer risk. Epidemiol Rev. 15:66; 1993.

Brinton, L.A.; Daling, J.R.; Liff, J.M. Oral contraceptives and breast cancer among younger women. J Natl Cancer Inst. 87(11):827; 1995.

Brownson, R.C.; Blackwell, C.W.; Pearson, D.K.; et al. Risk of breast cancer in relation to cigarette smoking. Arch Intern Med. 148:140; 1988.

Burch, J.C.; Byrd, B.F.; Vaughn, W.K. The effects of long-term estrogen on hysterectomized women. Am J Obstet Gyecol. 118:778; 1974.

Buring, L.E.; Hennekens, C.H.; Lipnick, R.J.; et al. A prospective cohort study of postmenopausal hormone use and risk of breast cancer in United States women. Am J Epidemiol. 125:939; 1987.

Bushberg, J.T.; Seibert, J.A.; Leidholdt, E.M. JR.; Boone, J.M. Mammography - Radiation Dosimetry for Mammography, pp 233 - 236, In: The Essential Physics of Medical Imaging. Williams and Wilkins. Baltimore, Maryland. 1994.

Cauley, J.A.; Cumming, S.R.; Black, B.M.; et al. Prevalence and determinants of estrogen replacement therapy in elderly women. Am J Obstet Gynecol. 163:1438; 1990.

Clifton, K.H.; Crowley, J. Effects of radiation type and role of glucocorticoid, gonadectomy, and thryoidectomy in mammary tumor induction in MtT - grafted rats. Cancer Res. 38:1507; 1978.

Cohen, M.; Jones, D.; Greene, D. Central axis depth dose data for use in radiotherapy. A survey of depth doses and related data measured in water or equivalent media. London: Br Inst Radiol; 1972.

Colditz, G.A.; Stampfer, M.J.; Willett, W.C.; et al. Prospective study of estrogen replacement therapy and risk of breast cancer in postmenopausal women. JAMA. 264:2648; 1990.

Colditz, G.A.; Hankinson, S.E.; Hunter, D.J.; et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. N Engl J Med. 332:1589; 1995.

Coleman, C.N. Secondary neoplasms in patients treated for cancer: Etiology and perspective. Radiat Res. 92:188; 1982.

Daling, D.R.; Brinton, L.A.; Voigt, L.F.; et al. Risk of breast cancer among white women following induced abortion. Am J Epidemiol. 144 (4):373; 1996.

Darby, S.C.; Doll, R.; Gill, S.K.; et al. Long term mortality after a single treatment course with x-rays in patient treated for ankylosing spondylitis. Br J Cancer. 55:179; 1987.

Davis, F.G.; Boice, J.D.Jr.; Hrubec, Z.; et al. Cancer mortality in a relation - exposed cohort of massachusetts tuberculosis patients. Cancer Res. 49:6130; 1989.

Donegan, W.L.; Spratt, J.S. Cancer of the Breast, third edition. W.B. Saunders Company. Philadelphia, Pennsylvania. 1988

Dupont, W.D.; Page, D.L. Risk factos for breast cancer in women with proliferative breast disease. N Engl J Med. 312:146; 1985.

Dupont, W.D.; Page, D.L. Breast cancer risk associated with proliferative disease, age at first birth, and a family history of breast cancer. Am J Epidemiol. 125:769; 1987.

Dupont, W.D.; Page, D.L. Relation to previous breast disease, In: Women at high risk to breast cancer. Stoll, B.A. (ed.), Kluwer Academic Pub., London, 1989.

Dupont, W.D.; Page, D.L.; Rogers, L.W.; et al. Influence of exogenous estrogens, proliferative breast disease, and other variables on breast cancer risk. Cancer. 63:948; 1989.

Dupont, W.D.; Page, D.L. Menopausal estrogen replacement therapy and breast cancer. Arch Intern Med. 151:67; 1991.

Ewertz, M. Influence of non-contraceptive exogenous and endogenous sex hormones on breast cancer risk in Denmark. Int J Cancer. 42:832; 1988.

Feur, E.J.; Wun, L.M.; Boring, C.C.; et al. The lifetime risk of developing breast cancer. J Natl Cancer Inst. 85:892; 1993.

Filipow, L.; AEC entrance skin exposures and average breast glandular dose measurement tables at a mammographic clinic; personal communication. February, 1997.

Freedman, L.S.; Prentice, R.L.; Clifford, C.; et al. Dietary fat and breast cancer: Where we are. J. Natl Cancer Inst. 85 (10):764; 1993.

Fry, R.J.M.; Ullrick, R.L. Combined effects of radiation and other agents. In: Radiation Carcinogenesis, pp 437 to 454. Upton, A.C.; Albert, R.E.; Burns, F.T.; Shore, R.E. (eds.), Elsevier, New York; 1986.

Gail, M.H.; Brinton, L.A.; Byar, D.P.; et al. Projecting individual probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst. 81:1870; 1989.

Gambrell, R.D.; Massey, F.M.; Castenada, T.A.; et al. Estrogen therapy and breast cancer in postmenopausal women. J Am Geriatr Soc. 28:251; 1980.

Gambrell, R.D.; Maier, R.C.; Sanders, B.I.; et al. Decreased incidence of breast cancer in postmenopausal estrogen-progestogen users. Obset Gynecol. 62:435; 1983.

Gapstur, S.A.; Potter, J.D.; Sellers, T.A.; et al. Increased risk of breast cancer with alcohol consumption in postmenopausal women. Am J Epidemiol. 136:1221; 1992.

Gentry, J.R.; Dewerd, L.A. TLD measurements of in vivo mammographic exposures and the calculated mean glandular dose across the United States. Med Phys. 23 (6):899; 1996.

Goodman, M.T.; Cologne, J.R.; Moriwaki, H.; et al. Risk factors for primary breast cancer in Japan: 8 - year follow-up of atomic bomb survivors. Prev Med. 26:144; 1997.

Greenland, S. Qualitative methods in the review of epidemiologic literature. Epidemiol Rev. 9:1; 1987.

Hammond, C.B.; Jelovsek, F.R.; Lee, K.L.; et al. Effects of long-term estrogen replacement therapy. Am J Obstet Gynecol. 133:537; 1979.

Harris, R.E.; Namboodiri, K.K.; Wynder, E.L. Breast cancer risk: Effects of estrogen replacement therapy and body mass. J Natl Cancer Inst. 84:1575; 1992.

Hayes, D.F.; Schnitt, S.J. Risk Factors, Epidemiology, and Development of Breast Cancer, In: Atlas of Breast Cancer, Hayes, D.F. (ed.), Wolfe, Boston, 1993

Heinrick, J.B. The postmenopausal estrogen / breast cancer controversy. JAMA. 268:1900; 1992.

Henderson, B.E.; Ross, R.; Bernstein, L.; Estrogens as a cause of human cancer: The Richard and Hinda Rosenthal Foundation Award Lecture. Cancer Res. 48:246; 1988.

Henderson, B.E.; Paganini-Hill, A.; Ross, R.K. Decreased mortality in users of estrogen replacement therapy. Arch Intern Med. 151:75; 1991.

Hennekens, C.H.; Buring, J.E. Epidemiology in Medicine. Little Brown and Company. Boston; 1987.

Hiatt, R.A.; Bawol, R.; Friedman, G.D. Exogenous estrogen and breast cancer after bilateral oophorectomy. Cancer. 54:139; 1984.

Hildreth, N.G.; Shore, R.E.; Dvoretsky, P.M; et al. The risk of breast cancer after irradiation of the thymus in infancy. N Engl J Med. 321 (19):1281; 1989.

Hoel, D.G.; Wakabayashi, T.; Pike, M.C. Secular trends in the distribution of the breast cancer risk factors - menarche, first birth, menopause and weight - in Hiroshima and Nagasaki, Japan. Am J Epidemiol. 118:78; 1983.

Hoffman, D.A.; Lonstein, J.E.; Morin, M.M.; et al. Breast cancer in women with scoliosis exposed to multiple diagnostic x-rays. J Natl Cancer Inst. 81:1307; 1989.

Hoover, R.; Gray, L.A.; Cole, P.; et al. Menopausal estrogens and breast cancer. N Engl J Med. 295:401; 1976.

Hoover R.; Glass, A.; Finkles, W.D.; et al. Conjugated estrogens and breast cancer risk in women. J Natl Cancer Inst. 67:815; 1981.

Horwitz, R.I.; Stewart, K.R. Effect of clinical features on the association of estrogen and breast cancer. Am J Med. 76:192; 1984.

Hosmer, D.W.; Lemeshow, S. Applied Logistic Regression. John Wiley & Sons Inc. New York; 1989.

Howe, G.R.; Hirohata, T.; Hislop, T.G.; et al. Dietary factors and risk of breast cancer: Combined analysis of 12 case-control studies. J Natl Cancer Inst. 82:561; 1990.

Hrubec, Z.; Boice, J.D.; Monson, R.R.; et al. Breast cancer after multiple chest fluoroscopies: second follow-up of Massochusetts women with tuberculosis. Cancer Res. 49:229; 1989.

Hulka, B.S.; Chambless, L.E.; Deubner, D.C.; Wilkinson, N.E.; Breast cancer and estrogen replacement therapy. Am J Obstet Gynecol. 143:638; 1982.

Hunt, K.; Vessey, M.; McPherson, K.; et al. Long-term surveillance of mortality and cancer incidence in women receiving hormone replacement therapy. Br J Obstet Gynaecol. 94:620; 1987.

International Commission on Radiological Protection, 1990 Recommendations of the International Commission on Radiological Protection, pub. 60, annex b - Biological effects of ionizing radiation; Stochastic Effects: Carcinogenisis, pp 106 to 114 and Estimates of probability for carcinogenic effects, pp 114 to 137. Smith, H. (ed), Pergamon Press, Oxford; 1991.

Iqbal, M.J.; Taylor, W. Hormonal and reproductive factors - New evidence, In: Women at high risk to breast cancer. Stoll, B.A. (ed.), Kluwer Academic Pub., London, 1989.

Jaffe, D.R.; Bowden, G.T. Ionizing radiation as an initiator in the mouse two-stage model of skin tumor formation. Radiat Res. 106:156; 1986.

Jaffe, D.R.; Bowden, G.T. Enhanced malignant progression of mouse skin tumors by ionizing radiation and activation of oncogenesis in radiation induced tumors. In: Radiation Research, Proceedings of the Eight International Congress of Radiation Research, Vol. 1. Taylor and Francis, Philadelphia; 1988.

Jenks, S. Breast cancer gene found. J Natl Cancer Inst. 86 (19):1444; 1994.

Jick, H.; Walker, A.M.; Watkins, R.N.; et al. Replacement estrogens and breast cancer. Am J Epidemiol. 112:586; 1980.

Kahn, H.A.; Sempos, C.T.; Statistical Methods in Epidemiology. Oxford University Press, Inc., New York; 1989

Kampert, J.B.; Whittemore, A.S.; Paffenbarger, R.S. Combined effect of childbearing, menstrual events and body size on age-specific breast cancer risk. Am J Epidemiol. 128:962; 1988.

Kaufman, D.W.; Miller, D.R.; Rosenberg, L.; et al. Noncontraceptive estrogen use and the risk of breast cancer. JAMA. 252: 63; 1984.

Kaufman, D.W.; Palmer, J.R.; de Mouzon, J.; et al. Estrogen replacement therapy and the risk of breast cancer: Results from the case-control surveillance study. Am J Epidemiol. 134:1375; 1991.

Kelly, P.T. Understanding Breast Cancer Risk. Temple University Press. Philadelphia, Pennsylvania. 1991.

Kelsey, J.L.; Fischer, D.B.; Holford, T.R.; et al. Exogenous estrogens and other factors in the epidemiology of breast cancer. J Natl Cancer Inst. 67:327; 1981.

Kelsey, J.; Berkowitz, G.; Breast Cancer epidemiology. Cancer Res. 48:5615; 1988.

Krieger, N.; Wolff, M.S.; Hiatt, R.A. Breast cancer and serum organochlorines: A prospective study among White, Black and Asian women. J Natl Cancer Inst. 86:589; 1994.

Kushi, L.H.; Sellers, T.A.; Potter, J.D.; et al. Dietary fat and postmenopausal breast cancer. J Natl Cancer Inst. 84 (14):1092; 1992.

Kushi, L.H.; Fee, R.M.; Sellers, T.A.; et al. Intake of vitamins A, C and E and postmenopausal breast cancer. The Iowa women's study. Am J Epidemiol. 144 (2):165; 1996.

La Vecchia, C.; Decarli, A.; Parazzini, F.; et al. Non-contraceptive oestrogens and the risk of breast cancer in women. Int J Cancer. 38:853; 1986.

Land, C.E.; McGregor, O.H. Breast cancer incidence among atomic bomb survivors: implications for radiobiologic risk at low doses. J Natl Cancer Inst. 62:17; 1979.

Land, C.E. Estimating cancer risks from low doses of ionizing radiation. Science. 209:1197; 1980.

Last, J.M (ed); Abramson, J.H.; Greenland, S.; Thuriaux, M.C. A dictionary of epidemiology. Oxford University Press. 1983.

Laya, M.B.; Gallagher, J.C.; Schreiman, J.S.; et al. Effect of postmenopausal HRT on mammographic density and parenchymal patterns. Radiology. 196:433; 1995.

Li, F.P.; Corkery, J.; Vawter, G.; et al. Breast carcinoma after cancer therapy in childhood. Cancer. 51:521; 1983.

Londen, S.J.; Willett, W.C. Relationship to diet and body size, In: Women at high risk to breast cancer, Stoll, B.A. (ed.) Kluwer Acad Pub. London; 1989.

Lynch, H.T.; Marcus, J.N.; Watson, P.; et al. Familial and genetic factors - New evidence, In: Women at high risk to breast cancer. Stoll, B.A. (ed.), Kluwer Academic Pub., London, 1989.

Mackenzie, I. Breast cancer following multiple fluoroscopies. Br J Cancer. 19:1; 1965.

MacMahan, B; Cole, P.; Brown, J.; Etiology of human breast cancer: A review. J Natl Cancer Inst. 50:21; 1973.

Mantel, N.; Haenszel, W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst. 22:719; 1959.

Mattsson, A. Ruden, B.I.; Hall, P.; et al. Radiation-induced breast cancer: Long term follow-up of radiation therapy for benign breast disease. J Natl Cancer Inst. 85:1679; 1993.

McGregor,D.H.; Land, C.E.; Choi, K.; et al. Breast cancer incidence among atomic bomb survivors, Hiroshima and Nagasaki, 1950 - 1969. J Natl Cancer Inst. 59:799; 1977.

Mettlin, C.; Schoenfeld, E. Effect of race, geography and social class, In: Women at high risk to breast cancer. Stoll, B.A. (ed.), Kluwer Academic Pub., London, 1989.

Miller, A.B.; Howe, G.R.; Sherman, G.J.; et al. Mortality from breast cancer after irradiation during fluoroscopic examination in patients being treated for tuberculosis. N Engl J Med. 321:1285; 1989

Mills, P.K.; Beeson, W.L.; Phillips, R.L.; et al. Prospective study of exogenous hormone use and breast cancer in Seventh - Day Adventists. Cancer. 64:591; 1989.

Mole, R.H. The sensitivity of the human breast to cancer induction by ionizing radiation. Br J Radiol. 51:401; 1978.

Moolgavhar, S.H.; Day, N.E.; Stevens, R.G.; et al. Two stage model of carcinogenesis: Epidemiology of breast cancer in females. J Natl Cancer Inst. 65:559; 1980.

Moolgavhar, S.H.; Knudsen, A.G. Mutation and cancer: A model for human carcinogenesis. J Natl Cancer Inst. 66:1037; 1981.

Morabia, A.; Bernstein, M.; Heritier, S.; et al. Relation of breast cancer with passive and active exposure to tobacco smoke. Am J Epidemiol. 143 (9):918; 1996.

Myrden, J.A.; Hiltz J.E. Breast cancer following multiple fluoroscopies during artificial pneumothorax treatment of pulmnary tuberculosis. Can Med Assoc J. 100:1032; 1969.

Nachtigall, M.J.; Smilen, S.W.; Nachtigall, R.D.; et al. Incidence of breast cancer in a 22 - year study of women receiving estrogen-progestin replacement therapy. Obstet Gynecol. 80:827; 1992.

Natarajan, N.; Nemoto, T.; Mettlin, C.; et al. Race-related differences in breast cancer patients: results of the 1982 national survey of breast cancer by the American College of Surgeons. Cancer. 56:1704; 1985

National Research Council, Committee on the Biological Effects of Ionizing Radiation; Health Effects of Exposure to Low Levels of Ionizing Radiation (BEIR V); National Academy Press; Washington D.C. 1990.

Newcomb, P,; Storer, B.E.; Longnecker, M.P.; et al. Lactation and a reduced risk of premenopausal breast cancer. N Engl J Med. 330:81; 1994.

Nomura, A.M.Y.; Kolonel, L.N.; Hirohata, T.; et al. The association of replacement estrogens with breast cancer. Int J Cancer. 37:49; 1986.

Ownby, H.E.; Frederick, J.; Russo, J.; et al. Racial differences in breast cancer patients. J Natl Cancer Inst. 75:55; 1985.

Palmer, J.R.; Rosenberg, E.A.; Clarke, D.R.; et al. Breast cancer risk after estrogen replacement therapy: Results from the Toronto breast cancer study. Am J Epidemiol. 134:1386; 1991.

Pike, M.C.; Krailo, M.D.; Henderson, B.E.; et al. 'Hormonal risk factors', 'breast cancer tissue age' and the age-incidence of breast cancer. Nature. 303:767; 1983.

Pike, M.C.; Spicer, D.V.; Dahmoush, L.; et al. Estrogens, progestogens, normal cell proliferation, and breast cancer risk. Epidemiol Rev. 15(1):17; 1993.

Ravnihar, B.; Seigel, D.G.; Lindtner, J. An epidemiologic study of breast cancer and benign breast neoplasms in relation to oral contraceptive and estrogen use. Eur J Cancer. 15:395; 1979.

Risch, H.A.; Howe, G.R. Menopausal hormones usage and breast cancer in Saskatchewan: A recored linkage cohort study. Am J Epidemiol. 139 (7): 670; 1994.

Rohan, T.E.; McMichael, A.J. Non-contraceptive exogenous oestrogen therapy and breast cancer. Med J Aus. 148:217; 1988.

Romieu, I.; Willett, W.C.; Colditz, G.A.; et al. Prospective study of oral contraceptive use and the risk of breast cancer in women. J Natl Cancer Inst. 81:1313; 1989.

Rosen, P.P.; Lieberman, P.H.; Braun, D.W., Jr.; et al. Lobular carcinoma in situ of the breast: detailed analysis of 99 patients with average follow-up of 24 years. Am J Surg Pathol. 2:225; 1978.

Ross, R.K.; Paganini - Hill, A.; Gerkins, V.R. A case-control study of menopausal estrogen therapy and breast cancer. JAMA. 243:1635; 1980.

Rossing, M.A.; Stanford, J.L.; Weiss, N.S.; et al. Oral contraceptive use and risk of breast cancer in middle-aged women. Am J Epidemiol. 144 (2):161; 1996.

Sartwell, P.E.; Arthes, F.G.; Tanascia, J.A.; et al. Exogenous hormones, reproductive history and breast cancer. J Natl Cancer Inst. 59:1589; 1977.

Schneider, T.; Hubert, D.; Degrange, J.P.; et al. Use of risk projection models for the comparison of mortality from radiation - induced breast cancer in various populations. Health Phys. 68 (4):452; 1995.

Sherman, B.; Wallace, R.; Bean, J. Estrogen use and breast cancer. Cancer. 51:1527; 1983.

Sherman, G.J.; Howe, G.R.; Miller, A.B. Organ dose per unit exposure resulting from fluroscopy for artificial pneumothorax. Health Phys. 35:259; 1978.

Shore, R.E.; Woodard, E.D.; Hempelmann, L.H.; et al. Synergism between radiation and other risk factors for breast cancer. Prev Med. 9: 815; 1980.

Shore, R.E.; Hildreth, N.; Woodward, E.; et al. Breast cancer among women given x-ray therapy for acute postpartum mastitis. J Natl Cancer Inst. 77:689; 1986.

Siegel, D.G. Frequency of live births among survivors of Hiroshima and Nagasaki atomic bombings. Radiat Res. 28:278; 1966.

Sillero-Arenas, M.M.; Delgado-Rodrigues, R.; Rodrigues-Canteras, A.; et al. Menopausal hormone replacement therapy and breast cancer: A meta-analysis. Obstet Gynecol. 79:286; 1992.

SPSS ® 6.1, Macintosh version; SPSS Inc. Chicago, Ilinois; 1994.

Stanford, J.L.; Thomas, D.B. Exogenous progestins and breast cancer. Epidemiol Rev. 15:98; 1993.

Stanford, J.L.; Weiss, N.S.; Voigt, L.F.; et al. Combined estrogen and progestin hormone replacement therapy in relation to risk of breast cancer in middle-aged women. JAMA. 274 (2):137; 1995.

Steinberg, K.K.; Thatcher, S.B.; Smith, S.J.l; et al. A meta-analysis of the effect of estrogen replacement therapy on the risk of breast cancer. JAMA. 265:1985; 1991.

Steinberg, K.K.; Smith, S.J.; Thacker, S.J.; et al. Breast cancer risk and duration of estrogen use: The role of study design in meta-analysis. Epidemiology. 5:415; 1994.

Stoll, B.A. Women at high risk to breast cancer. Kluwer Academic Pub. Dordrecht, 1989.

Storm, H.H.; Andersson, M.; Boice, J.D. Jr.; et al. Adjuvant radiotherapy and risk of contralateral breast cancer. J Natl Cancer Inst. 84:1245; 1992.

Swift, M.; Reitnauer, P.J.; Morrell, D.; et al. Breast and other cancers in families wit ataxia-telangiectasia. N Engl J Med. 316:1289; 1987.

Thomas, D.B.; Persing, J.P.; Hutchinson, W.B.; Exogenous estrogens and other risk factors for breast cancer in women with benign breast diseases. J Natl Cancer Inst. 69:1017; 1982.

Tokunaga, M.; Land, C.E.; Yamamoto, M.; et al. Incidence of female breast cancer among atomic bomb survivors, Hiroshima and Nagasaki. Radiat Res. 112:243; 1987.

Tokunaga, M.; Land, C.E.; Tokuoka, S.; et al. Incidence of female breast cancer among atomic bomb survivors, 1950 - 1985. Radiat Res. 138:209; 1994.

Tretli, S. Height and weight in relation to breast cancer morbidity and mortality: A prospective study of 570,000 women in Norway. Int J Cancer. 44:23; 1989.

Trichopoulos, D.; MacMahon, B.; Cole, P.; Menopause and breast cancer risk. J Natl Cancer Inst. 48:605; 1972.

Upton, A.C. Risk estimates for carcinogenic effects of radiation. In: Annals of the ICRP, Vol 22 (1), Risks Associated with Ionizing Radiation. Smith, H. (ed), Pergamon Press, Oxford; 1991.

Vorherr, H. Breast Cancer. Urban and Schwarzenberg. Baltimore, Maryland. 1980.

Weis, N.S.; Rossing, M.A. Healthy screenee bias in epidemiologic studies of cancer incidence. Epidemiology. 7 (3):319; 1996.

White, E.; Malone, K.E.; Weiss, N.S.; et al. Breast cancer among young United States women in relation to oral contraceptive use. J Natl Cancer Inst. 86(7):505; 1984.

White, E. Projected changes in breast cancer incidence due to the trend toward delayed childbearing. Am J Public Health. 77:495; 1987.

Willet, W.C.; Stampfer, M.J.; Colditz, G.A.; et al. Dietary fat and the risk of breast cancer. N Engl J Med. 316:22; 1987.

Willet, W.C.; Stampfer, M.J.; Colditz, G.A.; et al. Moderate alcohol consumption and the risk of breast cancer. N Engl J Med. 316:1174; 1987

Willett, W.C.; The search for the causes of breast cancer and colon cancer. Nature. 338:389; 1989.

Wingo, R.A.; Layde, P.M.; Lee, N.C.; et al. The risk of breast cancer in postmenopausal women who have used estrogen replacement therapy. JAMA. 257:209; 1987.

Wu, X.; Barnes, G.T.; Tucker, D.M. Spectral dependence of glandular tissue dose in screen-film mammography. Radiology. 179:143; 1991.

Wynder, E.L.; MacCornack, F.A.; Stellman, S.D.; The epidemiology of breast cancer in 785 United States caucasian women. Cancer. 41:2341; 1978.

Yong, L.C.; Brown, C.C.; Schatzkin, A.; et al. Prospective study of relative weight and risk of breast cancer: The Breast Cancer Detection Demonstration Project follow-up study: 1979 to 1987. Am J Epidemiol. 143 (10):985; 1996.

Zhang, Y.; Rosenberg, L.; Colton, T.; et al. Adult height and risk of breast cancer among white women in a case-control study. Am J Epidemiol. 143 (11):1123; 1996.

Zhou, X.; Gordon, R. Detection of early breast cancer: An overview and future projects. Crit Rev Biomed Eng. 17 (3):203; 1989.

Appendices

Appendix A Average Glandular Dose Determination

1. Calculation Method:

This method was used to determine the average glandular dose (AGD) associated with a mammographic exposure when information on kVp, mAs and compressed breast thickness (CBT) for the exposure is available. The form shown at the end of this section was used to calculate AGD from information provided on the mammogram and in the patient file. The AGD was calculated as follows:

1. The patient chart number was recorded.
2. The date (year/month) indicated on the mammogram was recorded.
3. The kVp, mAs and CBT indicated on the mammogram was recorded. If CBT information was not indicated on the mammogram, the average CBT value obtained from the other mammograms found in the patient chart were used. If no information was available on CBT, a nominal value of 4.5 cm was used.
4. Using figure 8 and the kVp value recorded in step 3, the X_a (mR) per mAs value associated with the exposure for a CBT of 4.5 cm was recorded.
5. The X_a per mAs value found in step 4 was multiplied by the mAs value found in step 3 and the resulting X_a (mR) value was recorded.
6. Using the inverse square law (Bushberg 1994) the skin entrance exposure (X_b) of the patient was calculated as follows:

$$X_b = X_a\,[(\mathrm{SID} - 4.5\ \mathrm{cm}) \div (\mathrm{SID} - \mathrm{CBT})]^2$$

where SID is the radiation 'source to image distance' (65 cm), CBT is the compressed breast thickness of the patient (cm), X_a is the skin entrance exposure for a nominal CBT value equal to 4.5 cm and X_b is the skin entrance exposure for the CBT value of the patient.

7. Using figure 9 and the CBT value found in step 3, the AGD / X (mrad per mR) value for the exposure was recorded.

8. The average glandular dose associated with the exposure was calculated as follows:

$$\mathrm{AGD\ (mrad)} = (X_b)(\mathrm{AGD}) / (X)$$

This value was recorded on the AGD calculation form.

2. Approximation Method:

This method was used to determine the average glandular dose (AGD) associated with a mammographic exposure when information on kVp or mAs for the exposure was not available. Figure 7 gives the AGD per mammogram received by women in the United States versus compressed breast thickness (Gentry 1996). The AGD value for the exposure was determined as follows:

1. The average CBT value of the patient from the mammogram CBT values found in the patient chart was calculted. If no CBT information was available for the patient, a nominal value or 4.5 cm was used.

2. From the average CBT value found in step 1, the AGD value associated with the exposure was determined using figure 7 and recorded on the AGD calculation form.

3. Cumulative Breast Dose Determination:

If the earliest reported mammogram was received outside of the study clinic, then the number of mammograms received prior to this exposure was unknown and it was not possible to determine the cumulative breast dose for the patient. However, if the earliest reported mammogram was received at the study clinic, then the cumulative breast dose could be calculated assuming that all subsequent mammograms were reported on the Patient History form.With this restriction in mind, the cumulative breast dose value was calculated by summing the individual AGD values of the exposures received at least 12 months prior to the reference pathology report date. This value was recored on the

AGD calculation form. For patients whose earliest recorded mammogram was received outside of the study clinic, '?' was recorded for the cumulative breast dose.

4. Average Glandular Dose Error:

A. Calculation Method:

The accuracy of calculating AGD depended on the accuracy of the indicated values of kVp, mAs and CBT. Assuming a worse case combination of + 0.5 kVp, + 5.0 mAs and

- 0.5 cm (Filipow 1997), the error in the AGD is calculated as follows:

Assumed Value + Error = Actual Value
27 kVp + 0.5 kVp = 27.5 kVp and
100 mAs + 5.0 mAs = 105 mAs and
4.5 cm - 0.5 cm = 4.0 cm

A. Assumed AGD
1. From figure 8: 27 kVp → 10.3 mR / mAs
2. Skin entrance exposure: (10.3 mR / mAs)(100 mAs) = 1030 mR
3. From figure 9: (1030 mR)(0.2 mrad / mR) = 206 mrad = assumed AGD

B. Actual AGD
1. From figure 8: 27.5 kVp → 11.0 mR / mAs
2. Skin entrance exposure (11.0 mR / mAs)(105 mAs) = 1155 mR
3. From figure 9: (1155 mR)(0.233 mrad / mR) = 269 mrad = actual AGD

Error = (Actual AGD - Assumed AGD) / Assumed AGD = (269 - 206) / (206)
= 0.31

Percent Error = 31 %

B. Approximation Method:

The maximum error in the estimation of AGD by the approximation method is probably greater than the maximum error using the calculation method since in the approximation method, x-ray machine data is unknown. However the patients used in the analysis of radiation risk received the majority of their mammographic exposures at the study clinic where x-ray machine data was available. Therefore the maximum error in the estimation of cumulative AGD should be similar to the maximum error in the estimation of AGD using the calculation method.

Average Glandular Dose Calculation Form

1. Chart Number:

2. Mammogram Date (year/month) :

3. kVp from mammogram :

4. mAs from mammogram :

5. CBT from mammogram :

6. mR/mAs @ 4.5 cm from figure 8 :

7. mR @ 4.5 cm = line 4 x line 6 :

8. $(58.5)^2 / (65 - \mathrm{CBT})^2$:

9. mR @ 65 - CBT = line 7 x line 8 :

10.mrad/mr @ CBT from figure 9 :

11.

a. AGD (mrad) = line 9 x line 10 :

or b. AGD (mrad) from figure 7 using average CBT :

12. Cumulative breast dose (mrad) = sum of all AGD values.

Appendix B Data Collection Instructions

1. Introduction:

A data collection procedure was used in this study to guide the data recorder in the abstraction of data from the Patient History Form, the pathology report, the radiology report and the mammograms. The same procedure was used for both cases and controls to help minimize observer bias in the study. The procedure began by obtaining information on all of the cases. After this was complete, the controls were selected and information was obtained on each of them. Biopsied cases used in the study were identified by a red tab and a green tab located on the edge of the patient chart. Biopsied controls used in the study were identified by a single green tab located on the edge of the patient chart. Charts with a red tab but no green tab identified patients with a previous history of breast cancer but which were not biopsied at the study clinic. These patient were not included in the study.

2. General Instructions:

Using the Patient Data Summary Form (PDSF) shown in figure 6, and the specific instructions given in section 3, the following steps were performed:

1. The sequence number was recorded.
2. The chart number was recorded.
3. The sex of the patient was recorded.
4. The patient's date-of-birth was recorded.
5. The information required on lines 22 - 26 were recorded.
6. The information required on line 5 was recorded.
7. The information required on line 21 was recorded.

For women age 60 and older with no record of prior breast cancer the following steps were completed.

9. The information required on lines 6 - 20 and 27 - 31 were recorded.

10. The information required for lines 32 - 33 was calculated.

3. Instructions for Completion of the Patient Data Summary Form:

A. Top row of the PDSF:

1. Sequence number (1 - 2000): Assign a sequential number to the patient beginning with 001 for the first patient chart. Record this number in the space provided on the PDSF.

2. Chart number (1 - 25000): Record the patient chart number found on the patient folder in the space provided on the PDSF. Verify that this number matches the number listed on the Patient History form.

3. Patient sex (f/m): Record the sex of the patient as 'f ' (female) or 'm' (male) that was indicated on the reference pathology report.

4. Date of birth (yr/mo): From the reference pathology report, record the year / month of birth in the space provided on the PDSF.

B. PDSF Columns (general information):

5. Patient History form date (yr/mo): Record the date of the Patient History form (year/month) in the space provided on the PDSF. If no date is indicated record '?' on the PDSF.

6. Age at menarche (y/?/nr): From the Patient History form, record the age to the nearest year of the patient's first menstrual period. If a question mark is given, record '?' on the PDSF. If no information is provided, record 'nr' (no response) on the PDSF.

7. Parity (number/nr): Record the number of live births indicated on the Patient History form. If no information is provided, record 'nr' on the PDSF.

8. Hysterectomy (yes/no/?/nr): Record 'yes' or 'no' on the PDSF. If a hysterectomy date is given, record 'yes' on the PDSF. If a question mark is given, record '?' on the PDSF. If no information is provided, record 'nr' on the PDSF.

9. Ovariectomy (uni/bi/no/?/nr): If one ovary was removed, record 'uni' on the PDSF. If both ovaries were removed, record 'bi' on the PDSF. If no ovaries were removed, record 'no' on the PDSF. If a question mark is given, record '?' on the PDSF. If no information is provided, record 'nr' on the PDSF.

10. HRT use (yes/no/nr): Record 'yes' in the space provided on the PDSF if yes, a type of hormone, or a length of time was indicated on the Patient History form. If none was indicated record 'no'. If no information is provided, record 'nr' on the PDSF.

11. HRT duration (months/na/nr): Record the HRT duration of use to the nearest month in the space provided on the PDSF. If no HRT use was indicated on the Patient History form, record 'na' (not applicable) on the PDSF. If a question mark is given, record '?' on the PDSF. If no information is provided, record 'nr' on the PDSF.

12. HRT type (name/na/?/nr): Record the name of the HRT used in the space provided on the PDSF. If no HRT use was indicated on the Patient History form, record 'na' on the PDSF. If a question mark is given, record '?' on the PDSF. If no information is provided, record 'nr' on the PDSF.

13. Other prescriptions (y/n/?/nr): If a positive response is given record 'yes'. If a negative response is given record 'no'. If a question mark is given, record '?' on the PDSF. If no information is provided, record 'nr' on the PDSF.

14. Family breast cancer (y/n/?/nr): Record 'yes' in the space provided on the PDSF if yes was indicated or if the age of the relative was indicated on the Patient History form. Record 'no' if none or no is indicated. If a question mark is given, record '?' on the PDSF. If no information is provided, record 'nr' on the PDSF.

15. Family non-breast cancer (y/n/?/nr): Record 'yes' if a positive response is indicated. Record 'no' if none is indicated.If a question mark is given, record '?' on the PDSF. If no information is provided, record 'nr' on the PDSF.

16. Personal non-breast cancer (type/n/nr): If a type of cancer other than breast cancer is indicated record the type. If no is indicated record 'no'. If only breast cancer is indicated record 'no'. If no information was provided, record 'nr' on the PDSF.

17. Referral source (s/ns/?): Record 's' in the space provided on the PDSF if the patient was referred to the study clinic from a mammography screening centre. Record 'ns' if the patient was referred to the study clinic from a referral source other than a screening centre. Record '?' on the PDSF if this information isn't provided in the patient chart.

C. PDSF Columns (breast specific information):

18. Current breast symptoms (y/n/nr): Record 'yes' in the column for the right or left breast if a positive response is given. If none is indicated record 'no'. If a positive response is given for one breast side but no response is given for the other breast side record 'no' for the breast in which no response is provided. If only a length of time is given but the breast side is not specified record '?' on the PDSF. If a question mark is given, record '?' on the PDSF. If no information is provided, record 'nr' on the PDSF.

19. Duration of symptoms (mos/na/?/nr): If a length of time is indicated for one or more symptoms, record the maximum duration in months for that breast side. If a duration is given but the breast side is not specified do not include that duration for consideration. If no is indicated in line 14, record 'na' on line 15 for the appropriate breast side. If the breast side is not specified for any symptom but a duration is given for one or more symptoms, record '?'. If no response is provided record 'nr' on the PDSF.

20.. Benign breast disease (y/n/?/nr): If cysts were drained or if breast surgery is indicated without the presence of breast cancer, record 'yes' on the PDSF. If yes is indicated for one breast side but no response is given for the other breast side, record 'no' for the other breast side. If the date of breast surgery is indicated but the breast side is not specified, record '?' on the PDSF. If no information is provided, record 'nr' on the PDSF.

21. Prior breast cancer (y/n/?/nr): If yes was indicated to 'Breast Cancer / Other Cancers' on the Patient History form determine what type of cancer was indicated. If breast cancer was indicated, record 'yes' for the appropriate breast side. If the breast side is not specified, record 'yes' for both breast sides. If a cancer other than breast cancer was indicated record 'no'. If cancer is indicated but not specified as to type record '?' If no response is given record record 'nr' on the PDSF. Record 'yes' on the PDSF if prior breast cancer is indicated on the reference pathology report or elsewhere in the patient chart.

22. Reference pathology report date (yr/mo): Record the date (yr/mo) of the reference pathology report on the PDSF.

23. Age-at-biopsy (yrs/mos): Record the age (yr/mo) of the patient that was indicated on the reference pathology report . Confirm this information by subtracting the patient's date of birth (year/month) from the reference pathology report date (year/month). Resolve discrepancies using other information in the patient chart.

24. Diagnosis (iv/is/b): Record 'iv' if an invasive breast cancer is indicated on the reference pathology report. Record 'is' if ductal or lobular carcinoma in situ is indicated without invasive breast cancer being present. Record 'b' (benign) if neither invasive or in situ breast cancer is indicated.

25. Tumour size (cm/?/na): If invasive breast cancer is diagnosed, record the size of the tumour to the nearest tenth of a centimeter. If invasive breast cancer is diagnosed

but the tumour size is not specified, record '?'. If invasive breast cancer is not diagnosed record 'na'.

26. Breast cancer stage (I/II/?/na): If invasive breast cancer is diagnosed but the reference pathology report indicates that the lymph nodes were not involved, record 'I' (stage I) on the PDSF. If lymph node involvement was indicated on the reference pathology report, record '' (stage II) on the PDSF. If the stage of disease is not specified on the reference pathology report, record '?'. If invasive breast cancer is not diagnosed, record 'na'.

27. Mammogram location (c/o): If the mammogram was performed at the study clinic record 'c' (clinic) on the PDSF. If the mammogram was performed outside of the study clinic record 'o' (other) on the PDSF.

28. Mammogram date (yr/mo/?): Record the date of the mammogram (yr/mo) on the PDSF. If the date is not indicated record '?' on the PDSF.

29. Mammogram voltage (kVp/?): Record the kVp of the mammogram on the PDSF. If the kVp is not indicated record '?' on the PDSF.

30. Mammogram current (mAs/?): Record the mAs indicated on the mammogram. Record '?' if this information is not indicated.

31. Mammogram compressed breast thickness (cm/?): Record the compressed breast thickness of the patient to the nearest tenth of a centimeter that is indicated on the mammogram. Record '?' if this information is not indicated on the mammogram.

32. Average glandular dose (mrad):

a) If kVp, mAs and CBT are known, use the 'calculation method' for determining average glandular dose found in Appendix A.

b) If kVp and mAs are known but CBT is unknown, use the 'calculation method' for determining average glandular dose found in Appendix A along with the average CBT value calculated on line 28 of the PDSF. If no CBT information is available, use 4.5 cm as the nominal value.

c) If kVp or mAs are unknown, use the 'approximation method' for determining average glandular dose found in Appendix A. Use the actual, estimated or nominal CBT value as appropriate.

33. Cumulative breast dose (mrad/?): Calculate the cumulative average glandular dose for each breast side of the patient using the method given in Appendix A.